PREVNAR 13

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Adult Indication

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ABBREVIATIONS

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Abbreviation	Definition
7vPnC	7-valent pneumococcal conjugate vaccine
9vPnC	9-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
23vPS	23-valent pneumococcal purified free-polysaccharide vaccine
ABCs	Active Bacterial Core surveillance
ACIP	Advisory Committee on Immunization Practice
ADR	adverse drug reaction
AE	adverse event(s)
AIDS	acquired immunodeficiency syndrome
ANCOVA	Analysis of covariance
CAP	community-acquired pneumonia
CAPITA	Community-Acquired Pneumonia Immunization Trial in Adults
CBER	Center for Biologics Evaluation & Research
CDC	Centers for Disease Control and Prevention
CDS	core data sheet
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
CRM_{197}	cross-reactive material 197 (nontoxic mutant form of diphtheria toxin)
CSF	cerebrospinal fluid
CSR	clinical study report
DMC	data monitoring committee
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition assay
HIV	human immunodeficiency virus
HPA	Health Protection Agency (United Kingdom)
ICF	informed consent form
IgG	immunoglobulin G
IgG1	immunoglobulin G subclass 1
IgG2	immunoglobulin G subclass 2
IgG3	immunoglobulin G subclass 3
IgM	immunoglobulin M
IPD	invasive pneumococcal disease
ITP	idiopathic thrombocytopenic purpura
LCI	lower limit of the 95% confidence interval

LIST OF ABBREVIATIONS

Abbreviation	Definition
LLOQ	lower limit of quantitation
MAI	mean avidity index
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
NCKP	Northern California Kaiser Permanente
NIP	national immunization program
NIS	Nationwide Inpatient Sample
NSAID	nonsteroidal anti-inflamatory drug
OPA	opsonophagocytic activity
PD	pneumococcal disease
PnC	pneumococcal conjugate vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
PS	Polysaccharide vaccines
RCDC	reverse cumulative distribution curve(s)
RR	relative risk
SAE	serious adverse event
SID	state inpatient databases
SOC	system organ class
TIV	trivalent inactivated influenza vaccine
UK	United Kingdom
US	United States
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VT	vaccine-type
WHO	World Health Organization
yo	years old

1.0 SUMMARY OF 13vPnC DEVELOPMENT RATIONALE FOR ADULT IMMUNIZATION AND OVERALL PROGRAM CONCLUSIONS

This section provides a summary of the underlying rationale for development of the 13-valent pneumococcal conjugate vaccine (13vPnC) for adult immunization and a summary of the clinical study data that confirm the rationale and, therefore, support the vaccine's proposed adult indication:

> "Active immunization for the prevention of pneumococcal disease (including pneumonia and invasive disease) caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults age 50 years and older."

In summary, the rationale and conclusions are as follows:

There is a medical rationale for a vaccine to prevent pneumococcal disease in adults 50 years of age and older.

- In adults beginning at 50 years of age, there exists a need for an effective vaccine to prevent pneumococcal disease, coincident with the increase in pneumococcal disease seen in the general population starting at this age (Sections 2.1, 2.4.5, 2.5).
- For individuals who have received the existing 23-valent free polysaccharide vaccine (23vPS), there exists a need for an effective vaccine to extend protection against pneumococcal disease for their entire lifetime of risk (Sections 2.1, 2.4.5).

The licensed 23vPS free polysaccharide vaccine is not suitable for meeting this medical need. While 23vPS has demonstrated efficacy against invasive pneumococcal disease (IPD) in controlled clinical trials, the vaccine has a number of limitations:

- Like other free (unconjugated) polysaccharide vaccines (PS), 23vPS induces a T-cell-independent immune response, and does not elicit immunologic memory. As a consequence, the duration of protection is limited to 3 to 5 years (Sections 2.2, 2.3, 2.4.1.1.2).
- 23vPS reimmunization has been associated with decreased antibody responses, compared to those after the first dose. Hence only a single dose of 23vPS is

recommended for adults over 65 years of age and vaccination is not generally recommended for adults 50 to 64 years of age. Therefore, 23vPS is limited in its ability to establish and maintain protection against pneumococcal disease over the perceived period of risk. (Sections 2.1, 2.2, 2.4.2).

- As a consequence, despite administration of 23vPS to 60% to 70% of adults ≥65 years of age for over 10 years, 23vPS has not reduced the overall disease burden in adults. (The only reductions in adult disease burden have occurred due to elimination of serotypes contained in 7vPnC [Prevnar®] after its introduction in children, presumed due to a herd immunity effect.)
- In addition, while 23vPS has been shown to be effective against IPD, its efficacy for prevention of pneumococcal community-acquired pneumonia (CAP) has been inconsistent. Clinical data supporting the vaccine's efficacy for CAP range from stronger, in the case of bacteremic pneumonia, to weaker, in the case of non-bacteremic pneumonia (Sections 2.4.3, 2.4.3.3).

Protein-conjugated pneumococcal polysaccharide vaccines (PnC) offer significant promise to provide improved protection against pneumococcal disease in adults.

- The best measurable immune response associated with the efficacy of pneumococcal vaccines is antibody-mediated opsonophagocytic activity (OPA, Section 3.1).
- PnCs elicit OPA immune responses in children and adults that are quantitatively and qualitatively superior to those elicited by PS. PnCs elicit a T-cell-dependent immune response and immunologic memory, increasing the potential for an anamnestic response on subsequent natural exposure and permitting revaccination to maintain or improve the functional anti-pneumococcal immune response, not achievable with the 23vPS vaccine (Section 2.4.1).
- The immunologic attributes of PnCs, including high antibody response and establishment of immunologic memory, have resulted in dramatic reductions in pneumococcal disease burden in children and adults. PnCs have been proven effective against IPD and pneumonia in children in developed and developing countries. Clinical studies in human immunodeficiency virus (HIV)-infected adult populations have provided evidence that conjugated vaccines exhibit notable efficacy against IPD and possibly pneumonia, in circumstances where 23vPS has not afforded such

protection to these immunocompromised adults. These observations provide support for the perspective that pneumococcal polysaccharide conjugate vaccine (PnC) is likely to protect against IPD and pneumococcal pneumonia in immunocompetent adults (Sections 2.4.3.3 and 2.4.4).

- Despite the potential indirect protection provided by pediatric PnCs in the United States, 13vPnC immunization of adults ≥50 years of age is necessary to ensure direct protection of adults against pneumococcal disease (Sections 2.3.3, 2.4.5).
- 13vPnC contains the serotypes most responsible for serious pneumococcal disease. These serotypes account for approximately 80% of the IPD that is currently covered by 23vPS. 13vPnC also contains serotype 6A, which is not contained in 23vPS.

Based on agreement with the FDA, the 13vPnC program was designed to demonstrate the immunological advantage of 13vPnC over that of 23vPS by OPA as a basis for accelerated approval and use in adults 50 years of age and older.

- Clinical studies were designed to support a single dose of 13vPnC for vaccination of pneumococcal vaccine-naïve adults to provide optimum protection against pneumococcal disease, and to support a single dose of 13vPnC for revaccination of 23vPS-experienced adults to extend protection (Sections 3.2, 3.3, 3.5). To accomplish these aims, the trials evaluated non-inferiority of OPA responses after 13vPnC compared to 23vPS, and superiority of response for serotypes in common.
- In addition, sequential vaccine studies were included to:
  - Provide evidence to support induction of immunologic memory after 13vPnC administration, not observed after 23vPS, and
  - Support the potential for 13vPnC revaccination to optimize protection over the lifetime of risk, not achievable with 23vPS.

  Data and analysis to define the appropriate interval for revaccination will be part of a subsequent application (Sections 3.3 to 3.5, 4.5.5).
- Based on agreement with the FDA, efficacy data against vaccine-type pneumococcal disease will be provided as a post-approval commitment, and such data are likely to be available by 2013 (Sections 2.5, 8.1.1).

The criteria for accelerated approval of 13vPnC in adults ≥50 years of age have been achieved and the results have demonstrated the following:

13vPnC is preferred to 23vPS for initial immunization of adults ≥50 years of age against pneumococcal serotypes most responsible for serious disease.

- In pneumococcal vaccine-naïve adults, 60 to 64 years of age, 13vPnC elicited OPA responses at levels that were non-inferior for all and statistically greater for 8 of 12 serotypes in common (and for serotype 6A not contained in 23vPS), compared to those elicited by 23vPS (Sections 4.3.1, 4.3.1.1, 4.3.1.2).
- In pneumococcal vaccine-naïve adults, 50 to 59 years of age, 13vPnC elicited OPA responses at levels that were non-inferior for all and statistically greater for 9 serotypes, compared to those elicited in subjects 60 to 64 years of age (Sections 4.3.1, 4.3.1.3, 4.3.1.4).

13vPnC is preferred to 23vPS for reimmunization of adults ≥65 years of age who have received 23vPS previously, to re-establish and maintain protection against pneumococcal serotypes most responsible for serious disease.

- In adults older than 70 years of age, who have been previously immunized with 23vPS, 13vPnC again elicited OPA responses that were non-inferior for all and statistically greater for 10 of 12 serotypes in common and serotype 6A, compared to those elicited by 23vPS. Over the following year, the OPA levels declined in both groups of recipients. However, a second study dose of 13vPnC generally resulted in recovery of OPA levels to those observed after the first study dose of 13vPnC. In contrast, subjects who had initially received 23vPS experienced a comparatively significantly lower OPA antibody response upon subsequent administration of 13vPnC, regardless of level of OPA response to 23vPS (Sections 4.3.2, 4.3.3, 4.4).

13vPnC should be given as the first pneumococcal vaccine whenever possible. For serotypes in common, an initial dose of 13vPnC has a clear positive effect on antibody responses to 23vPS administered 1 or 3.5 to 4 years later as well as on antibody

responses to a second dose of 13vPnC administered 3.5 to 4 years later. In contrast, a first dose of 23vPS vaccine has a noted negative impact on immune response to subsequent 23vPS or 13vPnC. The appropriate interval for 13vPnC reimmunization (13vPnC/13vPnC) to maintain protection is under investigation by Pfizer, but the data in the licensure application indicate that a repeat dose of 13vPnC can be administered as early as 3.5 to 4 years after the first dose and is clearly preferred to 23vPS/23vPS or 23vPS/13vPnC in pneumococcal vaccine-naïve adults.

- In pneumococcal vaccine-naïve adults, 60 to 64 years of age, the vaccine administration sequence of 13vPnC/23vPS resulted in OPA responses that were generally significantly greater for serotypes in common than levels seen following the reverse sequence of 23vPS/13vPnC (Sections 4.5.1).
- 13vPnC elicited statistically higher OPA responses to subsequent 23vPS administered at a 1-year or 3.5 to 4-year interval than were elicited by 23vPS alone for 6 of 12 or 9 of 12 serotypes in common, respectively, indicating 13vPnC establishment of memory and a booster response to serotype-specific polysaccharides. In contrast, OPA responses to 23vPS/23vPS spaced 3.5 to 4 years apart were statistically lower for 8 of 12 common serotypes after the second 23vPS dose, indicating a negative immunologic impact of 23vPS, and lack of establishment of immunologic memory (Sections 4.5.1 to 4.5.6).
- In this population, a second dose of 13vPnC administered 1 year after an initial dose of 13vPnC (ie, 13vPnC/13vPnC) did not result in full recovery for most serotypes of OPA geometric mean titer (GMT) levels to those observed after the initial 13vPnC administration. When the interval between 13vPnC/13vPnC was lengthened to approximately 3.5 to 4 years, the antibody responses to a second dose of 13vPnC were higher for most serotypes than those after the first 13vPnC dose. This is consistent with the perspective that generally high antibody levels maintained for 1 year after a first dose of 13vPnC limited the response to a second 13vPnC dose, but a longer dosing interval permitted the induction of comparable or, for most serotypes, statistically greater responses to a second dose. Importantly, 13vPnC/13vPnC antibody responses after the second dose were generally significantly greater than responses elicited by 23vPS/13vPnC or 23vPS/23vPS (Sections 4.5.1 to 4.5.6).

The quantitatively and qualitatively enhanced anti-pneumococcal immune responses elicited by 13vPnC in contrast to the responses elicited by 23vPS provide an increased likelihood that 13vPnC will demonstrate clear efficacy against serotype-specific pneumococcal CAP. Confirmation of efficacy will be obtained from the ongoing Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) trial. Final results are anticipated in 2013.

Co-administration of trivalent inactivated influenza vaccine (TIV) with 13vPnC was associated with comparable influenza antibody responses and lower 13vPnC antibody responses than when either vaccine was administered alone.

- TIV antibody responses were non-inferior for all 3 antigens when co-administered with 13vPnC vaccine in 50 to 59-year-old adults, compared to administration of TIV alone. In ≥65-year-old adults, the 95% lower confidence interval (CI) for the proportion of subjects with a ≥4-fold antibody response to H3N2 when TIV was co-administered with 13vPnC was slightly below (-10.4%) the predefined non-inferiority 95% lower CI of -10%, compared to administration of TIV alone. However, the proportion of subjects with HAI titers >40, also associated with protection, was high (96.5%) and within 1% of values in subjects who received TIV alone (97.4%). Responses in ≥65-year-old adults to H1N1 and B antigens were non-inferior after administration of concomitant 13vPnC and TIV compared to TIV alone (Section 4.6).
- Serotype-specific immunoglobulin G (IgG) and OPA immune responses to 13vPnC, co-administered with TIV, were generally lower compared to responses when 13vPnC was given alone, in adults 50 to 59 years of age and in adults ≥65 years of age. Therefore, concomitant administration of the 2 vaccines should be dictated by clinical circumstances (Section 4.6).

Local and systemic tolerability/safety assessments showed that the 13vPnC vaccine has a favorable safety profile.

- The safety and reactogenicity profile of a single dose of 13vPnC has been shown to be acceptable and comparable to 23vPS in 23vPS-naïve subjects (Sections 5.4, 5.4.2.1.1, 5.4.2.2.1, 5.4.2.2.2).

- Subjects preimmunized with 23vPS showed an improved reactogenicity profile after vaccination with a single dose of 13vPnC compared to revaccination with 23vPS (Sections 5.4, 5.4.2.1.4, 5.4.2.2.3).
- A second dose of 13vPnC given at a 1-year or 3.5 to 4-year interval is not associated with increased reactions (13vPnC/13vPnC) (Sections 5.4.2.1.5, 5.4.2.1.6, 5.4.2.2.4, 5.4.2.2.6).
- In contrast, administration of a study dose of 23vPS to adults ≥70 years of age previously immunized at least 5 years earlier with 23vPS showed higher local reactogenicity and an increase for some systemic reactions. Likewise, in younger adults, administration of 23vPS one year or 3.5 to 4 years after a dose of 13vPnC (13vPnC/23vPS) or 3.5 to 4 years after a prior dose of 23vPS, was associated with an increase in local reaction and sometimes systemic event rates. The common feature for each of these immunization regimens is receipt of 23vPS with its high pneumococcal polysaccharide load (25 µg for each polysaccharide) in a setting of pre-existing antibody from prior vaccination. This high polysaccharide load in the setting of prior antibody is likely to be responsible for the increased reactions seen (Sections 5.4.2.1.4, 5.4.2.2.3). Higher pre-existing antibody titers have been associated with increased reactions after 23vPS vaccine, whether present at the time of initial vaccination or at revaccination.[1]
- Subjects vaccinated with 23vPS followed 1 year later by 13vPnC (23vPS/13vPnC) showed an acceptable safety and reactogenicity profile (Sections 5.4.2.2.4, 5.4.2.2.6).
- Co-administration of 13vPnC with TIV was well tolerated, although somewhat more local and systemic events were observed in the younger subjects (50 to 59 years) compared to older subjects (≥65 years). Higher trends or statistically higher rates were seen for some systemic events after concomitant use, but were judged to fall within a satisfactory safety profile (Section 5.4.2.2.7).

The remainder of this briefing document will address each of the following in greater detail: the unmet medical need, the proposed indication, epidemiology, and burden of adult pneumococcal disease. This will be followed by a rationale for 13vPnC immunization of adults ≥50 years of age to meet the unmet medical need, and a description of the clinical program and results to support accelerated approval for this purpose.

2.0 PRODUCT DEVELOPMENT RATIONALE

2.1 Scientific Background: Unmet Medical Need

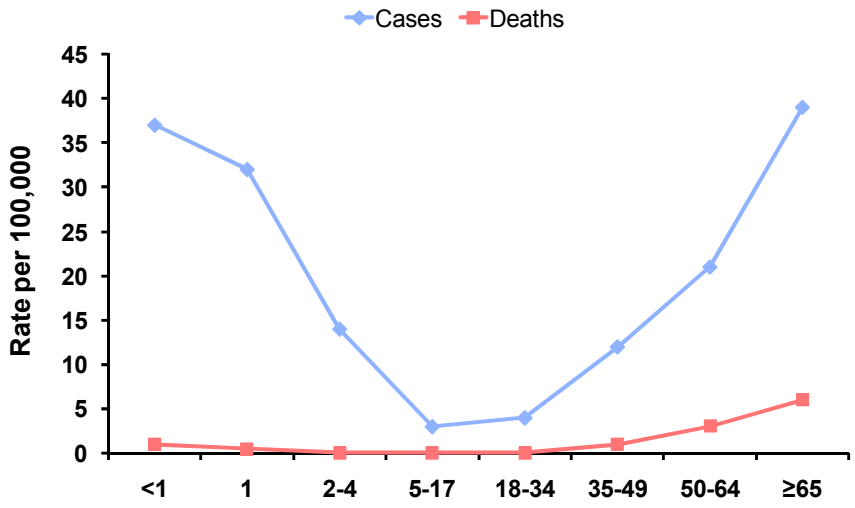
Pneumococcal disease can be classified by clinical presentation (invasive or noninvasive) and by risk factors (age, living circumstances, and underlying medical conditions). In adults, the clinical presentations of IPD include meningitis, bacteremia, and bacteremic pneumonia. IPD is defined by isolation of pneumococcus from a normally sterile site such as cerebrospinal fluid or blood, as well as pleural fluid or peritoneal fluid. Pneumonia without bacteremia is the most common serious manifestation of noninvasive pneumococcal disease.[2]

Adults older than 65 years and, increasingly, adults between 50 and 65 years of age are recognized to be at increased risk.[3,4] Residence in a nursing home or other long-term care facility can increase the individual risk of pneumococcal disease.[5] Significant medical risk conditions include: congenital or acquired immunodeficiency; sickle cell disease; asplenia; human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS); chronic heart, lung (including asthma), renal, or liver diseases; cancer; cerebrospinal fluid (CSF) leak; diabetes; chronic alcoholism or cigarette smoking; organ or hematopoietic cell transplantation; and cochlear implants.[6,7,8]

Vaccine-mediated protection against the spectrum of adult pneumococcal disease remains elusive despite considerable understanding of anti-pneumococcal immunology,[9,10,11] the availability and use of a 23-valent pneumococcal “free” polysaccharide vaccine (23vPS), and indirect protection (herd immunity) afforded by pneumococcal conjugate (PnC) administration in children.[12,13] In older adults, 23vPS appears to provide some protection against invasive pneumococcal disease (IPD), albeit of limited duration, and the ability of the vaccine to protect against pneumococcal community-acquired pneumonia (CAP) has not been consistently demonstrated.[13,14] Thus, an alternative vaccine that is effective in preventing pneumococcal CAP and that provides longer term protection for adults against IPD is considered highly desirable both by health agencies and by government authorities responsible for recommending vaccination programs.

The incidence of IPD is greatest at the extremes of life, creating a classic U-shaped curve of age versus incidence (Figure 2-1).[15]

Figure 2-1: *Streptococcus Pneumoniae* Incidence, 2009



Adapted from the US CDC, ABC surveillance, demonstrating rates of IPD.[15]

In addition to the disease burden in adults, the case-fatality rate from IPD among hospitalized patients remains high. In spite of advances in medical science over the last decades, the case-fatality rate (12% to 13% in the US, for instance) has remained constant through the 1950s to the present.[16,17,18,19,15]

The increasing burden of pneumococcal disease in the adult population older than 50 years of age underlies the interest in a pneumococcal vaccine strategy that could be initiated at age 50 years for pneumococcal vaccine-naïve healthy adults and that would extend protection for the large population of adults who have already received 23vPS vaccine.[13] However, for a variety of reasons, recommending bodies in many countries have resisted recommending the currently available 23vPS for adults younger than 60 to 65 years of age, except for defined high-risk groups, and typically have not recommended a formal revaccination strategy after 65 years of age except in those who received 23vPS prior to age 65, due to underlying risk

conditions.[4] Such restricted recommendations are driven by concerns that the immune response elicited by the free-polysaccharide vaccine is not particularly long lasting and that subsequent vaccination results in an immune response that is reduced in comparison to that achieved after the initial immunization.

2.2 Differences in Immune Responses to Native Polysaccharides and Polysaccharides Conjugated to Protein Carriers

It is known that the immune response to free polysaccharides is T-cell independent, resulting in immunity that is not long lasting and possibly limited in the breadth of the elicited antibody response.[20,21,22,23] In addition, the immune response to these vaccines does not appear to result in the establishment of B-cell memory, thereby limiting the ability to respond to multiple immunizations.[14] In young children, the free-polysaccharide vaccines fail to elicit an immune response. These characteristics have been consistently observed with all of the bacterial capsular free-polysaccharide vaccines, including the pneumococcal polysaccharides, the *Haemophilus influenzae* type b polysaccharide, and the meningococcal polysaccharides.[24,25,26]

In contrast, vaccines composed of bacterial polysaccharides that have been chemically conjugated onto an immunologically active "carrier" protein have been consistently capable of eliciting anti-polysaccharide antibody responses in young children, as well as in adults, characterized by longer lasting anti-bacterial antibodies and by the establishment of B-cell memory. The 7-valent pneumococcal conjugate vaccine (7vPnC, licensed as Prevnar® in the United States and as Prevenar® in most other countries) contains purified polysaccharides from 7 pneumococcal serotypes, each of which is chemically conjugated onto cross-reactive material 197 (CRM_{197}), a non-toxic, genetically modified, diphtheria toxin. This "conjugate" vaccine elicits a T-cell-dependent antibody response in children, resulting in the production of anti-pneumococcal functional opsonophagocytically active (OPA) antibodies that protect children against vaccine-type (VT)-IPD, pneumococcal CAP, and otitis media.[23,24,27] In addition, 7vPnC elicits functional opsonophagocytic antibody responses in older adults. In both children and adults, the 7vPnC responses can be maintained through revaccination.[28] Similar observations regarding maintenance of functional antibody responses have been

reported with polysaccharide conjugate vaccines for *H influenzae* type b and the meningococcus.[29,30,31]

Given the improved biological activity of the antibody response mediated by conjugate vaccines, public health authorities have expressed interest for some time in the possible development of such a vaccine for the long-term prevention of pneumococcal disease in adults. The recent licensure in children of a 13-valent pneumococcal conjugate vaccine (13vPnC, Prevnar 13® in the United States [US] and Prevenar 13® in most other countries) that contains the pneumococcal serotypes representing the most important causes of pediatric and adult disease worldwide has further stimulated this interest, resulting in the 13vPnC adult development program described herein.

2.3 Efficacy and Limitations of 23vPS

As reflected in the current US label indication for Pneumovax® (Merck &Co. Inc, Whitehouse Station, NJ), 23vPS is efficacious against pneumococcal disease as evidenced by controlled clinical trials, observational studies, and meta-analyses. However, duration of efficacy is limited to 3 to 5 years after a single dose, the T-cell-independent polysaccharide antigen fails to induce memory and is associated with decreased response to a second dose, and revaccination is not generally recommended for adults ≥ 65 years of age. Thus, although 23vPS has shown efficacy against IPD and against CAP (inconsistently) in controlled circumstances and thus can serve as an appropriate benchmark for evaluation of a new pneumococcal vaccine, effectiveness in open adult populations at risk has proved disappointing. Hence, there remains an unmet medical need for an improved vaccine that can induce robust durable antibody response and permits revaccination to reduce the adult pneumococcal disease burden. 23vPS indications, recommendations, and the data describing the efficacy and limitations of 23vPS are described in this section.

2.3.1 23vPS Indication and Recommended Use in Adults in the United States

The current US label indication for 23vPS (Pneumovax®, Merck & Co. Inc, Whitehouse Station, NJ) reads as follows:[32]

"PNEUMOVAX 23 is indicated for vaccination against pneumococcal disease caused by those pneumococcal types included in the vaccine. Effectiveness of the vaccine in the

prevention of pneumococcal pneumonia and pneumococcal bacteremia has been demonstrated in controlled trials in South Africa, France and in case-control studies.

PNEUMOVAX 23 will not prevent disease caused by capsular types of pneumococcus other than those contained in the vaccine.

Vaccination with PNEUMOVAX 23 is recommended for selected individuals as follows:
-routine vaccination for persons 50 years of age or older†
-persons aged ≥2 years with certain chronic conditions or in special environments or social settings."

† NOTE: The ACIP recommends routine vaccination for immunocompetent persons 65 years of age and older.

Based on review of the label indication and existing analyses of antibody response, safety, and efficacy, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practice (ACIP) updated its recommendations for use of 23vPS as reported in the Morbidity and Mortality Weekly Report in 2010.[33] The ACIP acknowledged the limitations of 23vPS, restricting recommended universal use to adults over 65 years of age and recommending against routine revaccination. Included in these recommendations is the following text:

"All persons should be vaccinated with PPSV23 at age 65 years. Those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years or later if at least 5 years have passed since their previous dose. Those who receive PPSV23 at or after age 65 years should receive only a single dose.

Revaccination. *ACIP recommendations for revaccination remain unchanged from the 1997 recommendations. For most persons for whom PPSV23 is indicated, ACIP does not recommend routine revaccination. A second dose of PPSV23 is recommended 5 years after the first dose for persons aged 19–64 years with functional or anatomic asplenia and for persons with immunocompromising conditions. ACIP does not recommend multiple*

revaccinations because of insufficient data regarding clinical benefit, particularly the degree and duration of protection, and safety."

A brief summary of the 23vPS efficacy data and limitations supporting the indication and recommended use are provided in the following sections.

2.3.2 Efficacy of 23vPS

2.3.2.1 Protection Against Invasive Pneumococcal Disease

The efficacy of 23vPS over a narrow interval of time is well established. In a combined analysis of 3 studies in young South African gold miners by Austrian and coworkers, purified pneumococcal free-polysaccharide vaccine was shown to reduce vaccine-type pneumococcal bacteremia by 82% and vaccine-type bacteremia and pneumonia combined by 78.5%.[34] Since 14-valent pneumococcal polysaccharide vaccine (14vPS) and subsequent 23vPS vaccine licensure, a number of additional controlled clinical trials[35,36,37,38,39,40,41,42] have been performed as reviewed by Fedson and Musher,[10] Jackson and Neuzil,[14] Makela and Butler,[43] Mangtani et al,[44] and Jackson and Janoff.[41] Findings support the value of purified free-polysaccharide vaccine in protecting adults against IPD and have estimated the efficacy against IPD caused by vaccine serotypes to be around 50%.[44, 45,46]

Given the difficulty of designing randomized controlled trials that are sufficiently powered to demonstrate the degree of protection afforded by 23vPS, investigators have performed numerous case-control and cohort observational studies to evaluate effectiveness against IPD and CAP. The history of these studies up to 2007 has been extensively reviewed.[41,14] In the majority of the studies reviewed, 23vPS reduced IPD in older adults.[47] In the largest indirect US CDC cohort study of 2837 cases in subjects 5 years of age and older, in which vaccine effectiveness was evaluated by comparing the distribution of vaccine serotypes in the vaccinated and unvaccinated groups, 23vPS effectiveness against IPD was estimated to be 57% (95% CI: 57%, 85%) in immunocompetent older adults.[46]

Recently, a small case-control study in Spain of 88 patients reported adjusted vaccine effectiveness of 77% (odds ratio: 0.23; 95% CI: 0.08, 0.60) against vaccine-type IPD, including significant effectiveness in adults over 80 years of age.[48]

To gain a consensus on 23vPS effectiveness and guide recommendations, several meta-analyses have been conducted. A recent Cochrane group review concluded: "The meta-analysis provides evidence supporting the recommendations for 23vPS to prevent IPD in adults."[49] The World Health Organization (WHO) reaches the following conclusion in a 2008 position paper based on evaluation of meta-analyses and a review of randomized controlled trials (RCTs): "On balance, as shown in the meta-analyses, the results of the RCTs of PPV23 are consistent with a protective effect against IPD and all-cause pneumonia among generally healthy young adults and, to a lesser extent, protection against IPD in the general population of elderly people." [6,50,49] In the same WHO position paper, now limited to an analysis of the observational studies, the conclusion was:

"…observational studies of the effectiveness of PPV23 generally have shown that the vaccine is 50–80% effective in preventing IPD among immunocompetent adults and individuals with various underlying illnesses who are not severely immunosuppressed."[6]

2.3.2.2 Protection Against Community-Acquired Pneumonia

The level of proof from observational studies that 23vPS can be effective in preventing adult CAP has ranged from stronger, in the case of bacteremic pneumonia, to weaker, in the case of non-bacteremic pneumonia. [49, 50, 51] In the same South African goldminer studies in which efficacy against IPD was convincingly demonstrated, Austrian and collaborators reported that purified pneumococcal free-polysaccharide vaccine reduced radiographically confirmed pneumonia by approximately 53%.[34]

Mayurama and collaborators[52] recently reported that 23vPS significantly reduced pneumococcal pneumonia (vaccine efficacy [VE] 63.8%, 95% CI: 32.1% to 80.7%) and all-cause pneumonia (VE 44.8%, 95% CI: 22.4% to 60.8%) in a selected population of elderly nursing home residents over a 2-year surveillance period. Over a 2-year surveillance period after vaccination in 1 report from Japan, 23vPS reduced the admissions for all-cause

pneumonia for subjects >75 years of age by 41.5% (p=0.039) and for those with difficulty walking by 62.7% (p=0.005), but not for all study subjects >65 years of age (p=0.183).[53]

It should be noted that in most studies of non-bacteremic pneumonia, the causative pathogen is not known and the study endpoint is generally "all-cause" CAP. This makes it difficult to unequivocally demonstrate the vaccine's effectiveness. If, for example, the pneumococcus is responsible for 30% of all-cause pneumonia, and the vaccine achieves 90% coverage and 50% efficacy, the observed all-cause pneumonia reduction would be <15%. Many studies and meta-analyses have not been powered to see a reduction of this magnitude. For example, regarding evaluation of efficacy against all-cause pneumonia, the authors of the Cochrane meta-analysis note: "the meta-analysis is inadequately powered to exclude a protective efficacy less than 48%. This has been a consistent criticism of previous meta-analyses that remains valid in this updated review." [49] Hence, 23vPS protects against pneumococcal pneumonia to some degree, but efficacy may be too low to consistently detect in the absence of a specific and sensitive test to identify non-bacteremic cases. The WHO summary of available controlled and observational studies observed that data to support 23vPS efficacy against pneumonia were inconsistent, but concluded "among recipients of PPV23 who nevertheless develop pneumonia, the severity of their illness and their risk of dying may be reduced."[6]

2.3.3 Limitations of 23vPS

23vPS efficacy wanes with advancing age, and the duration of efficacy is limited. In the largest, widely referenced case control study of 983 IPD cases by Shapiro et al,[45] 23vPS demonstrated 61% efficacy (95% CI: 47%, 72%) in immunocompetent adults with an indication for the pneumococcal vaccine, who were admitted to 1 of 11 hospitals in Connecticut. However, over time it is clear that the efficacy of the vaccine is limited. Prevention of IPD decreases with advancing age, and vaccine efficacy wanes by 3 to 5 years after vaccination (Table 2-1).

Table 2-1: Effectiveness of 23vPS Against Invasive Pneumococcal Disease in Adults, by Age and Time Since Vaccination

Age (years)	Time Since Vaccination		
	<3 Years	3-5 Years	>5 Years
	Vaccine Effectiveness, % (95% CI)		
<55	93 (82, 97)	89 (74, 96)	85 (62, 94)
55 - 64	88 (70, 95)	82 (57, 93)	75 (38, 90)
65 - 74	80 (51, 92)	71 (30, 88)	58 (-2, 83)
75 - 84	67 (20, 87)	53 (-15, 81)	32 (-67, 72)
≥85	46 (-31, 78)	22 (-90, 68)	13 (-174, 54)

Adapted From Shapiro et al as described by Jackson and Neuzil[14]

Despite evidence of efficacy under controlled circumstances and adult population vaccination rates over 70%, the reduced protection against IPD observed with advancing age and the lack of durable protection may account for the failure of 23vPS to show an impact on the overall rate of IPD. The US CDC has performed a comprehensive assessment of IPD burden beginning in 1997 prior to the introduction of 7vPnC, through introduction of a 7vPnC pediatric national immunization program (NIP) in 2000 that continues to the present. Before the introduction of pediatric 7vPnC, annual IPD rates were observed to climb at 35 years of age, and increase with each subsequent decade of life; death rates in adults 50 to 64 years of age were approximately two-thirds those of infants 1 year of age or less, and death rates in adults 65+ years of age were approximately 3 times those of infants 1 year of age or less. Immunization with 23vPS appears to have had no discernible effect on US rates of IPD, either based on CDC surveillance data or on population-based studies.[15,47] In Canada 23vPS did not reduce the death or hospitalization rate when administered to subjects, including those over 65 years of age, who had a history of an episode of hospitalized CAP.[54]

A recent summary of US disease burden is shown in Table 2-2.[55] It is notable that IPD and outpatient pneumonia in adults 50 to 64 years of age is over 50% of that observed in adults ≥65 years of age, and morbidity and death are frequent.

Table 2-2: Burden of Adult Pneumococcal Disease in the United States

Estimated Number of Cases	50 – 64 yrs	≥65 yrs
Invasive pneumococcal disease	11,297	18,155
Inpatient pneumococcal pneumonia (non-bacteremic)	33,749	164,852
Outpatient pneumococcal pneumonia (non-bacteremic)	104,494	199,526
Number of Deaths		
Invasive pneumococcal disease	1,762	4,415
Pneumococcal pneumonia requiring in-patient care	2,086	17,081

Weycker D et al. *Vaccine.* 2010;28:4955-4960.

To address this persistent unmet disease burden, repeat 23vPS vaccination is not an attractive option, as antibody responses 1 month after the second dose are decreased compared to those after the first dose, as observed by Torling,[56] Musher,[57] and Manoff,[58] presumably due to the inability of polysaccharide vaccine to establish memory. (This finding is also confirmed in the study 6115A1-004 extension of the current filing [see Section 4.5.5 for study summary].) Hence, the ACIP currently recommends universal immunization only for adults ≥65 years of age, and has been reluctant to extend routine immunization to adults ≥50 years of age, despite significant disease burden in this age group (see Section 2.3).

In contrast to the lack of 23vPS population-based effectiveness against IPD, 7vPnC NIPs in children have been associated with a reduction in adult pneumococcal disease due to vaccine serotypes in the US, but protection remains incomplete, and in some countries overall IPD burden remains unchanged. Introduction of infant and childhood 7vPnC immunization has resulted in a decrease in IPD in infants and toddlers and an indirect decrease in IPD in adults, which is presumed to be due to reduction of vaccine-serotype pneumococcal colonization in infants and lower likelihood of transmission to susceptible adults, referred to as indirect (herd) protection. In spite of this indirect protection, the gap in protection of adults in comparison to infants has widened.[15] In 2009, the mortality rate among adults 50 to 64 years of age (2.59/100,000) was more than 10-fold greater than the mortality rate among infants <2 years of age, and the mortality rate among adults ≥65 years of age (6.35/100,000) was 30-fold greater. In the US, despite the impact of pediatric 7vPnC in reducing IPD in all age groups by indirect protection, there are 44,000 IPD cases and 5000 deaths each year; the majority of these cases and deaths occur in adults over 50 years of age.[59,60, 61] Importantly, an indirect (herd) protection effect, leading to reductions in overall pneumococcal disease after childhood 7vPnC immunization, has not been universally observed. Rates of adult IPD in some countries, such as Denmark and Germany have remained relatively unchanged over the past 5 years, and rates in Spain have decreased but not yet to the degree seen in the US.[62,63,64]

In contrast to indirect reductions of IPD, including bacteremic pneumonia,[65] broad pediatric 7vPnC vaccination has yielded conflicting results about an indirect reduction of cases of CAP (pneumococcal or all cause), particularly in adults.[66, 67] Using an interrupted time-series analysis of data from the Nationwide Inpatient Sample (NIS), the largest US inpatient database available, Grijalva and colleagues[66] reported no significant indirect reductions from broad pediatric 7vPnC use, in either bacteremic pneumonia or all-cause CAP hospital admissions in adults 40 to 64 years of age or those ≥65 years of age. Nelson et al[67] conducted population-based pneumonia surveillance among 794,282 members of a private healthcare organization (Group Health Cooperative) before, during, and after introduction of infant and childhood 7vPnC. No reductions were seen for adults of any age in confirmed hospitalized pneumonia event rates after 7vPnC compared to periods before or during vaccine introduction. In fact, CAP hospitalization rates increased over time in some adult groups, particularly among seniors 75 years of age or more. Using Health Care Utilization Project

State Inpatient Databases (SID) for 1996 to 2006 from 10 states, Simonsen et al[68] reported a 54% (95% CI: 53-56%) reduction in non-bacteremic pneumococcal CAP in adults ≥65 years of age attributable to indirect protection from 7vPnC use but, somewhat paradoxically, were unable to demonstrate a statistically significant reduction in IPD in this age group. Serotype-specific information is not available in this dataset. Results are therefore mixed, and even if the most recent report by Simonsen is true, nearly 50% of the pneumococcal CAP burden remains.

Very little is known about the distribution of pneumococcal serotypes causing nonbacteremic CAP in adults. Despite a wider range of nasopharyngeal colonizing serotypes in vulnerable populations (such as HIV-infected adults[69] and Alaskan natives[70]), non-vaccine-serotype IPD and bacteremic pneumonia have been limited largely due to a few serotypes such as 19A and 7F (which are included in 13vPnC and not in 7vPnC). Hence, it is reasonable to expect that these serotypes are likely responsible for a sizeable proportion of remaining pneumococcal CAP, as they are for IPD. Furthermore, vaccine serotypes will continue to circulate globally and will continue to serve as a source of reintroduction to susceptible populations, particularly older adults. Outbreaks of pneumococcal disease in institutions for the elderly have been observed after introduction of virulent common serotypes (see also Section 2.4.5).[71] The risk of reintroduction and serious disease in a less immunocompetent older adult population might be expected to increase over time. This follows from the perspective that the potential for natural exposure and development of immune response at a more immuncompetent younger age can be expected to decrease in the US, due the reduction in circulation of conjugate pneumococcal vaccine strains, leaving these individuals progressively more vulnerable to serious pneumococcal infection as they age. Hence, there will continue to be a need for direct vaccination of adults against pneumococcal serotypes historically responsible for serious pneumococcal disease, even if pediatric pneumococcal immunization programs are associated with indirect protection against IPD and CAP.

Thus, there is an unmet medical need to develop an improved pneumococcal vaccine that can establish high functional antibody response and durable immunity and permit revaccination to improve upon the pneumococcal disease protection provided by 23vPS.

2.4 Rationale for Exploration of Adult 13vPnC for Prevention of Adult Pneumococcal Disease

The polysaccharide in the capsule of *S pneumoniae* is an important virulence factor and it is a target for immunologically mediated protection against pneumococcal disease. Serotype-specific antibodies that function as effective binders of complement and of Fcγ receptors are important mediators of this protection. However, experimentally and observationally defined protection afforded by T-cell–independent 23vPS against pneumococcal disease is incomplete (by age and by risk groups) and wanes over 3 to 5 years as noted in Section 2.3. Furthermore, the potential efficacy of 23vPS against pneumococcal CAP in older adults has not been consistently demonstrated. In addition, some studies have shown that 23vPS administration is associated with reduced immune responses to subsequent administration of 23vPS or pneumococcal conjugate vaccines.[28,57,58] Hence, only a single dose of 23vPS is generally recommended for unimmunized adults ≥65 years of age, and there has been reluctance to extend routine administration of 23vPS to adults over 50 years of age (Section 2.5). The ability to provide lifetime protection beginning at 50 years of age is compromised by the limitations of the 23vPS vaccine. Consequently, a significant burden of adult pneumococcal disease persists despite comprehensive 23vPS campaigns or broad pediatric 7vPnC immunization (Sections 2.1 to 2.3 and 2.4.5). There is a clear need for an alternative strategy.

Pneumococcal CRM_{197} conjugate vaccine (PnC) invokes T-cell–dependent immune mechanisms, with the potential for more robust opsonophagocytic antibody responses than those provided by T-cell–independent free-polysaccharide vaccine. Serum OPA titers after 7vPnC in adults are comparable to those of vaccinated children, and pneumococcal CRM_{197} conjugate vaccines have been demonstrated to protect children against pneumococcal pneumonia and IPD (7vPnC in Northern California Kaiser Permanente [NCKP] and the US NIS;[72,73,74] 9vPnC in Republic of South Africa[75] and The Gambia[76]); in addition, 7vPnC efficacy has been shown against vaccine-serotype IPD and possibly CAP in adolescents and adults infected with HIV.[77]

Cumulative experience with pneumococcal CRM_{197} conjugated vaccines predicts that 13vPnC immunization of adults should have the following advantages compared to 23vPS immunization:

- In pneumococcal vaccine-naïve adults and 23vPS-preimmunized adults, 13vPnC should induce higher antibody than 23vPS against most serotypes in common.
- 13vPnC administration should establish memory not possible with 23vPS administration.
- 13vPnC should permit revaccination for maintenance of optimum protection, not achievable with repetitive 23vPS immunization.
- The immunologic advantages of 13vPnC should confer protection against vaccine-type pneumococcal CAP (as well as IPD) not consistently observed with 23vPS.

With confirmation of these advantages, the inclusion of 13vPnC in an adult pneumococcal immunization program is likely to save lives beyond those now saved with the current, more limited 23vPS-based approach.[12,13] In addition to the enhanced immune response, a major life-saving benefit expected from 13vPnC will be the ability to extend the age range of protection against pneumococcal disease, beginning at 50 years of age in all adults and continuing beyond the seventh decade of life.[13]

2.4.1 Compared to 23vPS, 13vPnC is More Likely to Demonstrate Higher Functional Antibody in Adults, Induce Immunologic Memory, Promote Durable Protection, and Maintain and Improve Responses to Serotypes in Common

2.4.1.1 The Capacity for Functional Antibody Response to Free Pneumococcal Capsular Polysaccharide Decreases with Advancing Age

2.4.1.1.1 Immune Response to Vaccines in Older Adults

Immunosenescence of both innate and adaptive immune responses is characteristic of older adults. Immunological deficiencies with advancing age are observed from the point of initial contact with foreign antigen, during processing by dendritic and phagocytic cells, and with generation of humoral and cellular immunity.[78 79] Reduced numbers of early B-cell progenitors and intrinsic aging-associated defects lead to reduced or altered responses to extrinsic stimuli.[80,81,82,83, 84,85] The reserve of T cells that can effectively respond to novel antigens also declines with age.[86,87,88,89,90,91] The consequence is an overall decline in the

repertoire of available immune response to novel antigens, particularly polysaccharides. With respect to the pneumococcus, titers of antibodies to pneumococcal cell-wall and capsular polysaccharides declined significantly with increasing age in unvaccinated individuals aged ≥64 years.[92]

2.4.1.1.2 Nature of the Immune Responses to Capsular Polysaccharides

Administration of 23vPS has reduced potential to provide protection, in part because free-polysaccharides induce a T-cell–independent response. With few exceptions, free-polysaccharide antigens do not associate with major histocompatibility complex (MHC) class II antigens, and do not recruit classical cognate CD4+ T-cell help.[93,94] There are limited reactions in the germinal center (class switching, and somatic hypermutation) that could lead to affinity maturation or improved avidity.[20,21, 22,23,95, 96] As memory B cells are generally not induced by the free-polysaccharide antigens, re-exposure to 23vPS almost never leads to an anamnestic recall response.[14,85] Experimental evidence after 23vPS administration supports these expectations.[97, 98]

In addition, Romero-Steiner and colleagues from the US CDC have reported lower OPA responses after 23vPS in the elderly in comparison to younger adults, which correlate with lower antibody avidity.[99] In another study reported by Schenkein and members of Nahm's investigative group, IgG antibody titers against pneumococcal capsular polysaccharides (4, 6B, 9V, 14, 18C, 19F, 23F) were similar in adults aged ≤45 and ≥65 years following 23vPS vaccination, but antibody potency (the ratio of the OPA titer divided by the IgG antibody concentration) was significantly lower in the older group (2 to 8-fold lower).[100] In a follow-up study, more IgG antibodies were needed in the elderly to achieve an OPA titer of 1:8 for pneumococcal serotypes 4, 19F, 23F, and 6A, suggesting that, for these serotypes, the functional activity of antibody detected by the enzyme-linked immunosorbent assay (ELISA) was lower in the ≥65-year-old group compared with adults aged ≤45 years. Up to 30.3% (10 of 33) of the older subjects did not show opsonic activity for serotypes 4, 9V, 14, 19A and 6A after 23vPS vaccination.[101]

2.4.1.2 Pneumococcal CRM_{197} Conjugate Vaccine Is Better Suited Than 23vPS to Improve Functional Antibody Responses in Adults

When IgG antibody is produced after 23vPS, it is largely restricted to the IgG2 subclass, which binds complement and Fcγ receptors relatively poorly compared to other subclasses (IgG1, IgG3).[98] In contrast to the experience observed after purified free-polysaccharide vaccine, pneumococcal conjugate vaccine induces antibody subclasses with better OPA characteristics, and improved affinity maturation and avidity, in at least some circumstances.[23,102] Both IgG1 and IgG2 are increased, but the ratio of IgG1/IgG2 antibody is greater in adults after pneumococcal CRM_{197} conjugate vaccines.[98] Induction of IgG1 is consistent with T-cell–dependent response and establishment of memory. In addition IgG1 is a much more potent activator of complement and is known to interact more strongly with the Fcγ receptors (FcγRI, FcγRIIaHR allotype, FcγRIIb, and FcγRIIIc) on phagocytic cells than does IgG2.[103] Recently, Clutterbuck and collaborators have demonstrated that adults more efficiently establish polysaccharide-specific memory B cells than do 12-month-old toddlers, after administration of pneumococcal CRM_{197} conjugate vaccine. A single dose of 7vPnC is associated with effective generation of class switching and memory cells in adults; 2 doses of pneumococcal conjugate vaccine are required in toddlers to generate equivalent responses.[27] Hence, some capacity to generate new memory cells after conjugate vaccine persists with advancing age, and this should enable adults to make good functional antibody responses to conjugated pneumococcal polysaccharides.

It is challenging to discriminate memory recall versus primary response in pneumococcus-experienced adults. Clinical research in infants is instructive because it affords an opportunity to look at immunization of a population relatively naïve to natural pneumococcal exposure. In children, a sequence of 23vPS followed by 23vPS challenge immunization is associated with low IgG responses for most serotypes after the first dose, and no anamnestic response for any of the serotypes tested, consistent with the T-cell–independent nature of the free-polysaccharide antigens.[24,104,105,] Several studies have been performed in which infants were immunized with conjugate vaccines, followed by a polysaccharide vaccine (PS) challenge. Such evaluations of 7vPnC, 9-valent pneumococcal CRM_{197} protein conjugate vaccine (9vPnC), and an 11-valent protein conjugate vaccine have regularly shown anamnestic responses to PS challenge consistent with establishment of memory.[24,106,107]

Administration of pneumococcal CRM_{197} conjugate vaccine in infants followed by 23vPS challenge has been shown to induce both IgG1 and IgG2 response to tested 6B and 23F serotypes, compared with 23vPS primary immunization followed by 23vPS, which was associated primarily with an IgG2 response at a low level.[24]

Increases in antibody avidity after conjugate vaccine have been less compelling in adults than in infants. The presence of mature antibody at the time of adult immunization may result in only modest improvements in the mean avidity index (MAI). When IgG1, IgG2, OPA, and MAI were measured for serotypes 6B, 14, 19F, and 23F after different conjugate vaccines (diphtheria toxoid, tetanus toxoid, or CRM_{197}), responses tended to be higher compared to 23vPS for all outcomes but MAI in a combined analysis.[23]

2.4.1.3 Experimental Evidence in Pneumococcal Vaccine-Naïve Adults ≥70 Years of Age Confirms that 7vPnC Provides Immunologic Advantages Compared to 23vPS for Serotypes in Common

A study sponsored by Wyeth (a wholly owned subsidiary of Pfizer) in pneumococcal vaccine-naïve adults ≥70 years of age (study 6097A1-508 [D166-508]) evaluated administration of 7vPnC compared to 23vPS.[28] 7vPnC recipients received another vaccination with either 23vPS or a repeat dose of 7vPnC one year later. The 23vPS recipients were vaccinated 1 year later with 7vPnC. Results of this study are included as supportive data in the current submission (see module 5.3.5.4 Adult, study 6097A1-508 in submission). The experimental immunization scheme is shown in Figure 2-2.

Figure 2-2: Experimental Immunization Scheme --7vPnC Study in Adults ≥70 Years of Age

Study 6097A1-508

Study Design				
N	Dose 1	Dose 2 (at 1 year interval)	N	Total Regimen
110	7vPnC	7vPnC	43	(7vPnC/7vPnC)
		23vPS	38	(7vPnC/23vPS)
109	23vPS	7vPnC	78	(23vPS/7vPnC)

The study included evaluation of IgG antibody and OPA responses after a single dose of either 7vPnC or 23vPS and also evaluated the ability of 7vPnC to establish memory and improve 23vPS response 1 year later. Key findings[28] of this pilot study in pneumococcal vaccine-naïve adults ≥70 years of age were:

- 7vPnC elicited IgG and OPA antibodies at levels that were generally statistically significantly greater than those elicited by 23vPS for serotypes in common to both vaccines.
- The vaccine administration sequence of 7vPnC/23vPS (doses delivered a year apart) resulted in IgG and OPA antibody levels that were generally significantly greater than levels seen after an initial dose of 23vPS or following the reverse sequence of 23vPS/13vPnC, for serotypes in common to both vaccines. Some have speculated that this is due to terminal differentiation of antibody-producing cells; others have suggested that this phenomenon is due to suppressor cells.[108,109,110] In either case the result is consistent with the observations that purified free-polysaccharide vaccine induces antibody class and subclass responses with low opsonic potential, and poor memory.
- IgG and OPA responses after a second dose of 7vPnC (ie, 7vPnC/7vPnC), with doses spaced 1 year apart, were comparable to responses after the first dose.

These pilot study findings stand in marked contrast to the lower 1 month OPA responses observed after successive immunization with 23vPS,[57,58] and indicate that 7vPnC fundamentally enhances immune response to pneumococcal polysaccharide antigens on revaccination with 23vPS. Moreover, this pilot study established the premise that to achieve the full benefit of pneumococcal conjugate vaccine, it should be administered first in any regimen which also includes 23vPS.

In the 13vPnC clinical program, OPA and IgG responses after 13vPnC are compared to those after 23vPS in pneumococcal vaccine-naïve adults 60 to 64 years of age. In addition, sequential administration of 13vPnC and 23vPS is evaluated.

Recently, investigators reported additional data from the 6097A1-508 study in pneumococcal vaccine-naïve adults ≥70 years of age who received pneumococcal conjugate vaccine at a 1×(7vPnC only), 2×(7vPnC + 9vPnC), or 4×(2×7vPnC + 2×9vPnC) dose. There were no consistent or statistically significant differences in immune response between the standard 7vPnC dose (1×) and the 2×dose-level. The 4×dose-level elicited statistically higher antibody responses, but was associated with a higher incidence and greater severity of local reactions.[111]

These findings support the 0.5-mL 13vPnC dose licensed in children as the appropriate dose for investigation in pneumococcal vaccine-naïve adults.

Lazarus and colleagues have recently demonstrated statistically superior IgG responses after 7vPnC compared to 23vPS in adults 50 to 70 years of age, and a reduction of response to 7vPnC if it is preceded by 23vPS.[112] Statistical superiority of OPA response after a first dose of 7vPnC compared to 23vPS has now been replicated by Dransfield, Nahm and colleagues in adult patients (mean age 63) with chronic obstructive pulmonary disease.[113] These investigators administered 1.0 mL of vaccine, thus providing double the dose of pneumococcal conjugates as the standard 0.5-mL dose. When postvaccination to prevaccination antibody ratios were compared, serotype-specific IgG ratios were higher in

the 7vPnC group than the 23vPS group for all 7 serotypes and were statistically significantly higher for all but serotypes 14 and 19F ($p< 0.05$). Higher OPA to IgG ratios were also observed after 7vPnC for 6 of 7 serotypes (statistically significantly higher for 4, 9, 18C, and 23F) compared with 23vPS. Younger age and absence of prior 23vPS administration also were associated with increased OPA responses.

In contrast to the 508 study described above, Goldblatt and coworkers failed to demonstrate improvement in 23vPS IgG response when administered after 7vPnC at intervals shorter than 1 year (6 months between doses), whereas Lazarus and coworkers demonstrated increased IgG responses after 23vPS for serotypes 4, 9V, and 23F when it was preceded by 2 doses of 7vPnC spaced 6 months apart.[109 112] Sequential use of pneumococcal conjugate vaccine and 23vPS regimens with even shorter vaccination intervals did not result in additional improvement in IgG responses. In one small study, adults <45 years of age and adults >60 years of age received a pentavalent pneumococcal CRM_{197} conjugate vaccine followed by 23vPS two months later;[114] in another study, Alaskan natives received 7vPnC followed 2 or 6 months later by 23vPS (4, 6B, 14 and 19F).[115] A key finding for each of the studies evaluating a sequence of pneumococcal CRM_{197} conjugate vaccine followed by 23vPS is that the interval between doses of vaccine is important in relationship to response to a second dose (ie, the longer the interval, the greater the number of increased serotype-specific responses observed with the second dose). The likelihood of demonstrating an increased response for individual serotypes appeared to improve with an increase in dosing interval from 2 months to 6 months to 1 year. A possible explanation is that the level of functional antibody at the time of the second immunization impacts immune response to the second dose.

Although no long–term data are available on persistence of *protective* levels of antibody in pneumococcal conjugate–vaccinated adults, Mahdi and collaborators reported durable protection against IPD for >5 years in a vulnerable population of South African children, after a 3-dose priming series of a 9-valent CRM_{197} conjugate vaccine (9vPnC).[116] Efficacy against serotype-specific IPD was 77.8 % (95% CI: 34.4%, 92.5%) at 6.3 years. Whether protection is purely due to persistence of antibody or recall upon natural re-exposure is unclear. However, taken together these results indicate persistence of protection from a

conjugate in the absence of booster immunization after the infant series and offer promise for durable immunity and protection after pneumococcal conjugate vaccine in adults.

Hence, protection against infection may persist after immunization with conjugate vaccine; defining the administration interval of 13vPnC followed by either 13vPnC or 23vPS will be important in determining how best to maintain response in adults over 50 years of age for the lifetime of the individual.

Other observations from early studies with 7vPnC or 9vPnC in adults were as follows: IgG responses were 10% lower for every 10 years of advancing age in adults;[109] little difference was noted in the kinetics of B-cell responses in a small study (with authors acknowledging that that much larger cohorts will be required to permit robust comparison of the potential of different vaccine formulations to recruit circulating memory B-cell populations);[117] and the best predictor of subsequent circulating B cells in conjugate or free-polysaccharide vaccine recipients was not the type of vaccine received but the level of binding antibody prior to immunization.[118] However, functional antibody response, as determined by OPA, was not evaluated in these studies, so the relationship of vaccine type to functional memory response was not experimentally described.

2.4.2 13vPnC Reimmunization of Adults Previously Immunized With Either 23vPS or 13vPnC is Likely to Extend Protection Better Than 23vPS Reimmunization

As noted in the studies by de Roux and Lazarus,[28,112] immune responses to 7vPnC administered 6 months or 1 year after 23vPS were reduced in comparison to responses after 7vPnC alone. This reduction in response reinforces concerns about a negative immunologic consequence to administration of 23vPS as a first dose resulting in reduced responses to a second dose of 23vPS in the same subjects, as described by Torling.[56] In another study, Musher and collaborators examined separate populations who received 1 or 2 doses of 23vPS and compared responses.[119] At 1 month, serotype-specific IgG responses were generally lower after revaccination compared to primary vaccination, and statistically lower for 2 of 8 serotypes tested. By 3 to 5 years IgG antibody levels were comparable. A companion study by Manoff analyzed a subset of sera for OPA responses to 3 serotypes, and revealed similar findings.[58] These investigators have recently reported IgG findings but not OPA responses,

over a 10-year interval after repeat 23vPS vaccination.[120] While noting that these studies are limited by comparison of separate non-randomized populations, IgG antibody rises were seen after a second or third dose at 10 years compared to predose and baseline values; nonetheless, antibody levels at 30 days after the last dose were generally lower than those 30 days after the prior dose, indicating a potential effect of advancing age or negative impact of prior 23vPS immunization.

The level of circulating antibody persisting after immunization may also be an imprecise measure of durable protection. The ability to respond effectively with an anamnestic response to natural pneumococcal challenge may be critical for protection. The observed decrease in serotype-specific binding 1 month after repeat 23vPS immunization compared to initial immunization remains and is consistent with other such observations. Given the T-cell-independent characteristics of free-polysaccharide antigen, as noted by Musher and colleagues as contributing to decreased duration of protection,[120] this difference may represent a fundamental deficiency in the ability to generate memory and the capacity for recall. The ability to facilitate recall response may be key to protection, and is an expected immune response of CRM_{197} conjugate vaccine. By conjugating the polysaccharides to CRM_{197}, T cells are stimulated and immune memory is likely to be induced.[27,121]

The finding of reduced immune response after either 23vPS/7vPnC or 23vPS/23vPS sequential administration, in addition to the observation that in older adults initial 7vPnC results in an increased response to subsequent 23vPS administration (for serotypes in common to both vaccines), provide mounting evidence that pneumococcal CRM_{197} conjugate vaccine should be administered first whenever possible to optimize potential benefits. However, there is a large population of older adults worldwide (eg, >60% and >70% of adults over 65 years of age in the USA and UK, respectively) who have already received 23vPS according to current recommendations. In light of the apparent negative consequences of a first dose of 23vPS upon successive vaccination with either conjugate or free-polysaccharide vaccine, it is important to determine whether a subsequent vaccination with 13vPnC affords an advantage over reimmunization with 23vPS to extend protection. Moreover, as noted in Section 2.5 above, the FDA has recognized extension of protection in adults previously immunized with 23vPS as a key unmet medical need. Published evidence

from Jackson and collaborators suggests that CRM_{197} pneumococcal vaccine does afford such an advantage with the standard 0.5 mL dose used in children.[122]

These observations provide important guidance regarding factors to consider in evaluation of immune response after 13vPnC in adults: comparison of immune response to 23vPS response in vaccine-naïve and 23vPS-experienced adults, relationship of age to immune response, evaluation of durability of immune response, response to 13vPnC/23vPS and 13vPnC/13vPnC revaccination as a measure of memory, and dosing interval required to maintain immunity, all including functional OPA response as the key measure. These factors are investigated in the 13vPnC adult clinical program.

2.4.3 13vPnC Is Likely to Provide Better Protection in Adults Against Pneumococcal Community-Acquired Pneumonia (CAP) Compared to 23vPS

2.4.3.1 Pneumococcal Conjugate Vaccine Protects Immunized Children Against CAP

2.4.3.1.1 Clinical Trials of 7vPnC or 9vPnC Against Pediatric CAP

The unambiguous success of CRM_{197} conjugate pneumococcal vaccines in preventing IPD and pneumococcal CAP in children offers the promise of efficacy against CAP in adults. In the pivotal efficacy study conducted in pediatric populations served by Northern California Kaiser Permanente (NCKP), episodes of clinically diagnosed pneumonia with a positive radiograph in 7vPnC-vaccinated children were reduced by 20.5% (95% CI: 4.4%, 34.0%, p=0.02, per protocol analysis) compared to findings in unvaccinated children. The greatest impact was in the most vulnerable children: a 32.2% reduction in the first year of life and a 23.4% reduction in the first 2 years. Ten (10) of the 11 cases of bacteremic pneumococcal pneumonia were in the control group.[72,73] Using a World Health Organization (WHO) standardized method of scoring chest radiographs, a revised analysis revealed 30.3% (95% CI: 10.7%, 45.7%, p=0.0043, per protocol analysis) efficacy against a first episode of radiograph-confirmed pneumonia.[74] In the pediatric study conducted by Klugman and colleagues in South Africa, 9-valent pneumococcal CRM_{197} conjugate vaccine reduced the incidence of first episodes of radiograph-confirmed alveolar consolidation by 25% (95 % CI: 4% to 41%; per protocol analysis) in children without HIV infection.[75] In a study in the Gambia, 9-valent pneumococcal CRM_{197} conjugate vaccine (9vPnC) efficacy was 37% (95% CI: 27%, 45%) against a first episode of radiological pneumonia.[76]

2.4.3.1.2 Effectiveness of 7vPnC Against Pediatric CAP

7vPnC has also proven effective against CAP in immunized children in population-based observational studies. As previously noted in Section 2.3.3, Grijalva et al performed an interrupted time-series analysis of the US NIS that compared pneumonia admissions from a period prior to 7vPnC introduction (1997-1998) to a period after introduction (2001-2004).[66] By the end of 2004, all-cause pneumonia admissions in children less than 2 years of age had declined by 39% (95% CI: 22%, 52%) resulting in a calculated reduction of 41,000 US pneumonia admissions. For children younger than 2 years of age, coded as having pneumococcal pneumonia, rates declined by 65% (95% CI: 47%, 77%). In Australia, where children are administered a 3-dose series of 7vPnC without a toddler booster dose, there were significant adjusted reductions in all-cause pneumonia in children aged <2 years and 2 to 4 years of 38% (95% CI: 36%, 40%) and 29% (95% CI: 26%, 31%), respectively.[123] These findings offer promise that 13vPnC will provide a similar benefit in adults.

2.4.3.2 13vPnC Is Likely to Protect Adults Against Pneumococcal CAP Better Than 23vPS Based on Functional Antibody Responses Comparable to Those Observed in Vulnerable Pediatric Populations Protected Against Pneumonia by Conjugate Vaccine

The immunologic attributes of CRM_{197} conjugate pneumococcal vaccine, including establishment of memory, combined with strong evidence of efficacy against pneumonia in children, encourage expectations of a similar benefit in adults. The Wyeth sponsored 6097A1-508 randomized study of 7vPnC and 23vPS in adults ≥70 years of age, and serologic results from study 140-1 in infants, permitted a comparison of OPA responses in these 2 groups using identical OPA assays.[124,125] (The OPA assays used in the 13vPnC adult trials were modified from those used in the 13vPnC pediatric program; hence, direct titer comparisons of 13vPnC responses in infants and adults are not possible.)

In naïve elderly the OPA values for each of the 7 serotypes before vaccination with either 7vPnC or 23vPS were substantially lower than those achieved in infants less than 1 year of age vaccinated with 3 doses of 7vPnC (Table 2-3). After vaccination of adults ≥70 years of age with 23vPS, OPA GMTs for 6 of 7 serotypes remained substantially below those of 7vPnC-immunized infants <1 year of age. Therefore, after 23vPS the elderly, in general, are

not able to achieve functional antibody titers that are as large as those associated with protection against IPD and pneumonia after 7vPnC immunization in children.

In contrast, after initial immunization with 7vPnC, OPA GMTs in adults ≥70 years of age exceeded those seen after 23vPS for 6 of 7 serotypes and approximate the OPA levels seen in infants after 3 doses of 7vPnC (Table 2-3).[28,124,125] These findings suggest that 7vPnC offers a potential advantage over 23vPS in producing functional levels of antibody that are comparable to those in infants protected against IPD and CAP. This should translate to a higher likelihood of protection against both IPD and pneumococcal CAP in adults after 13vPnC compared to 23vPS.

Table 2-3: Comparison of OPA GMTs in Vaccine-Naïve Infants and Adults

Type	Infants Post 3 Doses 7vPnC	Elderly Post 1 Dose 7vPnC	Elderly Post 1 Dose 23vPS
4	1571	1503.8	669.9
6B	1888	1351.2	809.2
9V	3551	2914.6	984.6
14	3017	2164.8	974.5
18C	1559	1317.5	464.6
19F	203	182.2	202.7
23F	4846	1309.3	302.4

2.4.3.3 13vPnC Is Likely to Provide Better Protection in Adults Against Invasive Pneumococcal Disease and Pneumococcal Community-Acquired Pneumonia than 23vPS, Based on Efficacy of 7vPnC in HIV-Infected Adults

Pneumococcal CRM_{197} conjugate vaccine has been shown to protect HIV-infected African adults and adolescents against IPD and demonstrated a trend for protection against all cause

CAP. This contrasts to the failure of 23vPS to protect against IPD and pneumonia in a similar African HIV-infected population.[77,126]

In a large randomized placebo-controlled trial in young Ugandan adults suffering from HIV infection conducted by Neil French and collaborators, 23vPS was ineffective against first event IPD. A total of 1392 HIV-infected adults were randomized to receive 23vPS or placebo.[126] Nearly half of subjects had a CD4 cell count below 200, consistent with significant immunocompromise. Surprisingly vaccine-type IPD (VT-IPD) and all-cause pneumonia were actually greater in the vaccine group than the placebo group during the first 6 months of follow up (VT-IPD relative risk [RR] 4.91, 95% CI: 1.07, 22.39; all-cause pneumonia RR 2.82, 95% CI: 1.19, 6.66), and were not statistically different from the control group after the prescribed 2.5 years of follow up (VT IPD RR: 1.48, 95% CI: 0.65, 3.32; all-cause pneumonia RR 2.02, 95% CI:1.19, 3.45). A longer-term follow-up study for a total of 6 years from enrollment failed to show a statistically significant benefit for protection against VT-IPD or all-cause pneumonia, although a trend was noted for reduced relative risk of death at 6 years (RR 0.84, 95% CI: 0.7, 1.0).[127]

Neil French and coworkers[77] have subsequently evaluated the efficacy of 7vPnC in 496 Malawian adolescents and adults who had recovered from documented IPD. In this double-blind, randomized, placebo-controlled clinical efficacy trial, 2 doses of vaccine were given 4 weeks apart, and subjects were observed for a median follow-up time of 1.2 years (range, 2 days to 4.7 years). There were 67 episodes of pneumococcal disease in 52 HIV-infected patients; in 24 subjects, 19 episodes were caused by vaccine serotypes and 5 episodes were caused by the 6A serotype. Of these 24 episodes, 5 occurred in the vaccine group and 19 in the placebo group, for a vaccine efficacy of 74% (95%CI: 30%, 90%).

These results stand in marked contrast to the Ugandan experience. The failure of 23vPS to protect HIV-infected Ugandan adults was shown to be associated with suboptimal immune response to serotypes in the vaccine and diminished vaccine serotype-specific antibody concentrations in cases of IPD, as measured by IgG binding antibody.[128,129] In contrast, the investigators demonstrated significant rises in serotype-specific IgG antibody after 1 dose and again after a second dose of 7vPnC in 23vPS-naïve and -experienced HIV-infected

Ugandan adults.[130] The protection afforded against IPD in the Malawian trial is consistent with this greater response.

Possible Reduction of All-Cause CAP in the Malawian Trial

In the Malawian trial,[77] the investigators also explored rates of all-cause pneumonia and identified an unadjusted lower rate of pneumonia of 0.75 (95% CI: 0.47, 1.19) in the vaccine group compared to the control group. Although this result did not achieve statistical significance, it revealed a very promising trend for reduction of CAP in an immunocompromised population (baseline average CD4 count 212 in 7vPnC recipients, 214 in placebo recipients). Assuming that vaccine-type pneumococcal pneumonia (VT-CAP) could reasonably account for 25% to 50% of CAP in this population at high risk for pneumococcal reinfection, the fractional reduction of CAP due to vaccine-type pneumococcal infection would be high (50% to 100% reduction of VT-CAP) if the point estimate is, in fact, correct. The study was limited by sample size and the lack of specific and sensitive testing for nonbacteremic VT-CAP that could have confirmed such a result.

Hence, 7vPnC demonstrated efficacy against IPD and possibly against VT-CAP in a significantly immunocompromised population, in similar circumstances to those for which 23vPS failed to provide protection. These findings have important implications for pneumococcal immunization of older adults. Like HIV-infected adults but to a lesser degree, older adults demonstrate reduced immune response to 23vPS, compromising efficacy of 23vPS against IPD and precluding protection against VT-CAP. Like HIV-infected adults but to a greater degree, older adults appear to have better immune responses to CRM_{197} conjugate pneumococcal vaccines. Given the ability of CRM_{197} pneumococcal vaccine to protect against IPD and possibly VT-CAP in HIV-infected adults, it is therefore highly likely that 13vPnC will provide at least similar, if not better, protection against such pneumococcal disease in HIV-negative adults.

Evaluation of the ability of 13vPnC to protect against CAP in adults is a post-licensure commitment under the accelerated approval process, and results from the CAPiTA study addressing this unmet medical need are anticipated by 2013.

2.4.4 13vPnC is Likely to Provide More Comprehensive Protection Than 23vPS Against Serotypes Responsible for Serious Pneumococcal Disease

Despite the inherent deficiencies of 23vPS in providing protection, and the improved functional antibody responses to be expected after 13vPnC, it is inevitable that comparisons will be made between expected serotype coverage afforded by 13vPnC and 23vPS. However, these comparisons should not be based purely on the number of serotypes in the respective vaccines. Rather, the serotypes most responsible for pneumococcal disease need to be considered based upon an understanding of serotype-specific virulence and the burden of disease that exists despite the use of the polysaccharide vaccine.

2.4.4.1 13vPnC Serotypes Responsible for Adult Invasive Pneumococcal Disease

The serotype-specific epidemiology of adult IPD has been studied based on isolates from otherwise sterile sites of patients suffering from pneumococcal diseases such as meningitis, bacteremia, or bacteremic pneumonia.

In the US, the distribution of IPD serotypes in adults >65 years of age can be compared from 1998-1999 (pre-7vPnC) to 2006-2007 (post-7vPnC).[131] The 13vPnC coverage fell from 75.5% to 49.9%, which can be attributed to the indirect (herd) effect of the childhood NIP for 7vPnC that began in 2000-2001. The most prevalent serotypes in 2006-2007 (each having a frequency greater than 7%) were 19A, 6A, 3, 7F, and 22F.

In England and Wales, unpublished surveillance data from the United Kingdom (UK) Health Protection Agency (HPA) reveal the effect of a targeted 23vPS program (2003 to 2006) in elderly adults and the impact of the 7vPnC NIP that began in 2006.[132] In the first period, there was little change in the proportion of isolates covered by 23vPS (from 88.8% in 2002-2003 to 87.8% in 2005-2006). This absence of impact was equally noted among the 13 serotypes in 13vPnC (from 72.5% in 2002-2003 to 74.0% in 2005-2006) and the 11 serotypes unique to 23vPS (from 20.4% in 2002-2003 to 18.5% in 2005-2006). The contrast is striking once 7vPnC was introduced into the NIP in 2006, as there was an important change in the proportion of serotypes associated with 13vPnC (from 74.0% in 2005-2006 to 52.6% in 2009-2010), among the most prevalent remaining serotypes being 19A, 3, 22F, and 7F. By

contrast, the proportion of serotypes unique to 23vPS rose (from 18.5% in 2005-2006 to 29.2% in 2009-2010).

In the US, the coverage of the 23vPS vaccine was estimated to be 87.9% in the early 1980's when the vaccine was first being introduced.[133] According to the CDC ABC surveillance, the coverage of 23vPS was 88% in 18 to 64 year olds and 84.1% in >65 year olds in 1998 to 1999.[131] This suggests that despite extensive use of the vaccine, especially in >65 year olds, there was no impact on proportion of IPD caused by the 23 serotypes.

2.4.4.2 Particular Virulence of the 13vPnC Serotypes

The 13 serotypes contained in 13vPnC are not only responsible for most IPD episodes, but many of these capsular serotypes are more likely to be associated with serious illness and death, compared to other serotypes.

Recent studies have followed adult pneumococcal disease patients in order to identify those serotypes most likely to be responsible for outcomes such as mortality, hospitalization (in particular, a more severe hospital course), or more serious IPD (ie, meningitis or bacteremia without a focus).

Serotypes 3, 14, 19F, 4, 11A, 1, 23F, 12F, 9V, 9N, 6B, 6A, and 19A figure prominently as important causes of disease most responsible for serious disease and death in 2 Danish studies, and serotype 3 emerged as a particularly virulent serotype.[134, 135] Thus, based on the Danish experience spanning 1990 to 2007, 13vPnC includes 10 of the 13 serotypes most responsible for serious disease.

A retrospective cohort study of hospitalized IPD patients in the Netherlands (June 2004 to May 2006) evaluated the invasive disease potential of pneumococcal serotypes.[136,137] The case-fatality rate was elevated for serotypes 3, 6B, 9N, 16F, 18C, 19F, 23A; for elevated case-fatality rate and/or prolonged hospitalization (>19 days), the most important serotypes were 3, 6B, 9N, 18C, 22A, 22F, 23F, and 33F.

Sjostrom et al evaluated results from 2 prospective clinical studies of IPD in adult patients (5 nations, 1993 to 1995, and Stockholm) that also linked severity with particular serotypes.[138] In previously healthy individuals who had APACHE II scores >11, serotypes 3, 6A, 6B, 19A, and 19F were infecting the majority of these patients. Elevated case-fatality rates (ie, above the medium, 14% [11% to 17%]) were linked to serotypes 3 (32%), 6A (33%), 6B, 11A, and 19F. In particular, "case-fatality rates of patients infected with serotypes 6B, 11A, 19F, 3, and 6A, in ascending order, ranged from 19% to 33%." In previously healthy individuals, "serotypes 3 and 6B were associated with the highest mortality," about 30%.

Similarly, many of these same serotypes were identified in other studies. For instance, Lexau, et al in the US, looking at adults >50 years with IPD, uncovered a higher case-fatality rate for serotypes 3, 11A, 19F, and 23F (versus serotype 14, reference).[59] By contrast, in another multinational study,[139] "neither serotypes defined as invasive or pediatric, nor 7vPnC serotypes, were associated with a higher mortality rate."

In an 8-study meta-analysis from the US, Europe, Africa, and the Middle East, bacteremic pneumonia caused by serotypes 3, 6A, 6B, 9N, and 19F was more lethal in adults and children (compared to serotype 14), while the relative risk was likewise increased for serotypes 19A and 23F (but not statistically significantly).[140] Bacteremic pneumonia caused by serotypes 3, 6A, 6B, 9N, and 19F was more lethal in adults and children (compared to serotype 14), while the relative risk was likewise increased for serotypes 19A and 23F (but not statistically significantly).

2.4.4.3 Conclusions Regarding Potential Protection Afforded by 13vPnC Compared to 23vPS

A limited number of serotypes are responsible for the virulent IPD in adults. The serotypes of 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) are most often identified among adult IPD patients, and are commonly found identified as pneumococcal serotypes associated with higher morbidity and mortality rates. A few other serotypes beyond these 13 are also of note (8, 9N, 11A, 12F, 15C, 24F), but these serotypes account for a small proportion of the adult IPD disease burden. Some are not contained in either 23vPS or 13vPnC (15C and 24F),

and evidence of 23vPS serotype-specific effectiveness is lacking for others (8, 9N, 11A, 12F).

The serotypes contained in 13vPnC account for 77% of the pneumococcal disease covered by the serotypes in 23vPS in adults over 65 years of age.[131] If functional immune responses after 13vPnC can be shown to be non-inferior to 23vPS for all and statistically significantly greater for some serotypes, and 13vPnC demonstrates advantages for generation of immunologic memory and potential for revaccination, 13vPnC is likely to provide greater and more sustainable protection than 23vPS against the serotypes most responsible for serious disease.

2.4.5 Despite the Potential Indirect Protection Provided by Pediatric Pneumococcal Conjugate Vaccines in Some Regions, 13vPnC Immunization of Adults ≥50 Years of Age is Necessary to Ensure Protection Against Pneumococcal Disease

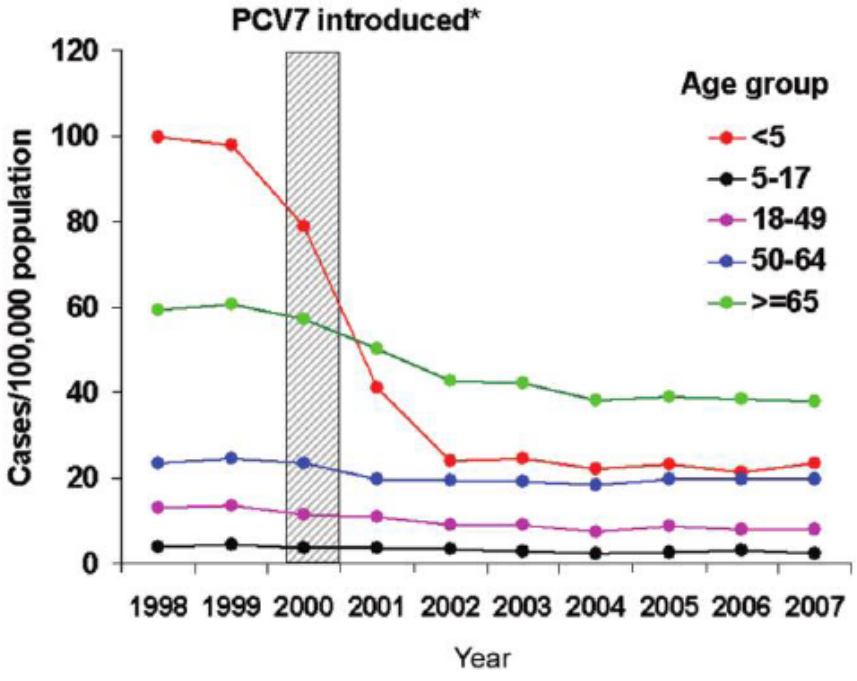
As noted previously, a national infant and childhood 7vPnC immunization program has resulted in indirect reduction of pneumococcal disease over a 7-year period in older children and adults in all age groups, including adults over 65 years of age in the United States.[65,131] This is presumed to be due to significant reduction of carriage and transmission of disease-carrying serotypes from the pediatric population. 13vPnC immunization of infants and children is expected to reduce disease in the vaccinated population due to targeting the 6 additional vaccine serotypes and may also reduce carriage and transmission. However caution should be exercised in extrapolating the US 7vPnC experience to 13vPnC and other settings. Results have been mixed in European countries as described in Section 2.3.3, which may be related to variations in the 7vPnC vaccination programs (primary and booster dose uptake, and application of "catch-up" immunization campaigns) between countries.

In the US where indirect protection has proven most dramatic, pneumococcal disease reduction in non-vaccinated populations increased gradually over 7 years after inception of a 7vPnC infant national immunization program (NIP) (Figure 2-3, see also Section 2.4.4.1). It is estimated that in adults over 50 years of age, there are 29,500 cases of IPD, 500,000 cases of non-bacteremic pneumococcal pneumonia, and 25,400 related deaths annually.[55] Even in the setting of a herd effect from infant immunization with 13vPnC, it is estimated that vaccinating adults over 50 years of age with 13vPnC would prevent an additional 17,400

cases of IPD, 1.5 million cases of pneumococcal pneumonia, and 90,000 deaths, relative to the current 23vPS vaccination program. Revaccination at a 10-year interval would result in estimated reductions of an additional 52,000 cases of IPD, 2.6 million cases of pneumonia, and over 170,000 deaths. [141]

The total number of residual cases in older adults is at least several-fold higher than the number of cases in the infant population for which 13vPnC is currently indicated. As noted in Section 2.3.3, the mortality rate by 2009 among adults 50 to 64 years of age (2.59/100,000) was more than 10-fold greater than the mortality rate among infants <2 years of age, and the mortality rate among adults ≥65 years of age (6.35/100,000) was 30-fold greater. IPD attack rates in adults over 65 are now the highest of all age groups, and the total burden of illness in adults over 50 years of age greatly exceeds that of other age groups.[131]

Figure 2-3: Rates (%) of Invasive Pneumococcal Disease by Age Groups, USA, 1998/1999 to 2007



In addition, due to the worldwide distribution of pneumococcal serotypes, and the low likelihood of worldwide eradication, susceptible populations remain vulnerable to reintroduction of disease-causing strains. It is surmised that natural protection against pneumococcal disease develops over a lifetime of exposure to pneumococci. As immune responsiveness wanes in older age, the capacity to respond to pneumococci is diminished. The absence of pneumococcal serotype circulation in a population over time could leave older adults particularly at risk, because they will be naïve to exposure at a younger age when immune response is more robust and less likely therefore to mount an anamnestic response at the time of exposure following reintroduction of a vaccine-associated serotype. This is more than a theoretical risk. Introduction of novel pneumococcal serotypes into a nursing home setting has been associated with serious outbreaks of pneumococcal disease and death.[71] Gleich et al[142] reported one such outbreak in New York City, and reviewed 26 reported pneumococcal disease outbreaks occurring before 7vPnC introduction; more than half of these worldwide epidemics involved older adults in hospitals or long-term care facilities.[71,143] In the New York City nursing home outbreak, pneumonia developed in 18 of 200 residents (9%) over a 2-week period. Four (4) patients died. *S pneumoniae*, serotype 4, was isolated from the blood cultures of 3 patients; pulsed field gel electrophoresis patterns of the 3 isolates were indistinguishable. A pneumococcal etiology was diagnosed in a total of 11 residents (61%) with the addition of sputum culture and serology. A subsequent CDC report in 2001 described a nursing home outbreak in New Jersey, which included 7 blood culture isolates of serotype 14 pneumococcus of the identical England 14-9 clonal group.[143] Serotypes 23F, 14, and 4 accounted for 67% of the reviewed US outbreaks, speaking to the particular virulence of these serotypes when introduced into an institutional setting. Since it is unlikely that these serotypes will be eradicated on a global basis, and their potential for virulent spread in institutional settings is well established, institutional populations that are not vaccinated with 13vPnC are likely to be at particular risk for serious pneumococcal disease.

In summary, whether childhood 13vPnC leads to gradual reduction of vaccine-strain carriage and transmission or whether it does not, older unimmunized adults are left vulnerable to introduction and disease outbreaks due to the most significant disease-causing serotypes.

Hence, older adults are likely to benefit from direct immunization regardless of any indirect benefit of pediatric 13vPnC immunization.

2.5 Use of the Accelerated Approval Regulation for Initial Licensure in the US

During discussions with the US FDA, it was acknowledged that there is a significant unmet medical need for an alternative pneumococcal vaccine in adults ≥50 years of age due to the burden of pneumococcal disease in this age group. This need is particularly pronounced in adults age 65 and older who have already received the 23vPS vaccine.

Prior to the start of phase 3 clinical trials, the FDA determined that the accelerated approval regulation (21 CFR 601.41) was an appropriate regulatory pathway for conditional licensure of 13vPnC for adults ≥50 years of age. In the agency's official response to the pre-supplemental BLA meeting held on October 15, 2010, the Center for Biologics Evaluation and Research (CBER) confirmed that the marketing application could be submitted based on the accelerated approval regulatory pathway. The decision to use the accelerated approval mechanism reflected the high rate of life-threatening pneumococcal pneumonia in the elderly and the demonstrated potential of 13vPnC to provide clinical benefit over the currently available 23vPS vaccine, which is approved for use in adults for the prevention of pneumococcal disease caused by the serotypes in the vaccine. The accelerated approval regulation is designed to make promising therapeutic agents, including vaccines and drugs, available for use more quickly (ie, expedited marketing) where the product provides meaningful therapeutic benefit compared to existing products for a serious or life-threatening disease. Therefore, the FDA agreed that the initial conditional licensure for subjects ≥50 years of age could be based on immunogencity endpoints rather than on clinical efficacy, namely, the induction of anti-bacterial opsonophagocytic activity antibody (OPA, a surrogate marker reasonably likely to predict efficacy). Full licensure would then be sought post-approval based on confirmation of clinical efficacy.

Since 23vPS has been shown to have some efficacy against IPD and pneumonia, albeit limited in terms of both rate and duration, the agency agreed that demonstration of a similar or higher OPA response after 13vPnC vaccination in comparison to 23vPS, in both pneumococcal vaccine-naïve and non-naïve individuals, would support conditional approval

for protection against pneumococcal disease. Importantly, additional clinical benefits of the immune response elicited by the conjugate vaccine were required for evaluation to support initial licensure. To this end, the effect of vaccine administration sequence (eg, 13vPnC/23vPS vs 23vPS/13vPnC) was studied to assess potentially significant qualitative differences in the anti-pneumococcal immune responses elicited by 13vPnC compared to the responses elicited by 23vPS, including differences in the ability to elicit memory response. As part of these added evaluations, successive administrations of the same vaccine (13vPnC/13vPnC and 23vPS/23vPS) were also evaluated to assess the potential for maintenance of the anti-pneumococcal response by revaccination with the conjugate vaccine compared to the free-polysaccharide vaccine. Data for 13vPnC/13vPnC, 13vPnC/23vPS and "on study" 23vPS/23vPS sequences, with a 3 to 4 year interval between doses, were provided in an amendment to the supplemental BLA.

Accordingly, in the US (as well as in the European Union [EU] following similar regulatory interactions) a clinical development program comparing the OPA antibody responses elicited by 13vPnC to those elicited by the licensed 23vPS, combined with an evaluation of vaccine administration sequence and revaccination, was accepted to support initial approval of an adult indication. The indication for the 13vPnC vaccine is expected to be similar to the current label indication for the 23vPS vaccine (ie, the prevention of vaccine-type pneumococcal disease[VT-PD]), plus acknowledgement of the accelerated approval status. Consistent with the accelerated approval regulations, the FDA required that 13vPnC be assessed in a phase 4 efficacy trial to confirm its effectiveness using the prevention of vaccine-type community-acquired pneumonia (VT-CAP) as the primary objective. It was also agreed with the agency that effectiveness of 13vPnC against IPD would be assumed based on satisfactory demonstration of a comparable or higher functional antibody response compared to 23vPS in the phase 3 clinical program. The pneumonia efficacy study with 13vPnC is fully enrolled and ongoing in The Netherlands. Following approval of this initial BLA supplement for 13vPnC in adults, the results from the efficacy study will be submitted as a follow-on supplement. The efficacy trial is event-driven and it is currently anticipated that the study will reach its primary endpoint within the next 2 years. This trial is further described in the Appendix, Section 8.1.1.

2.6 Proposed Indication

To address the unmet medical need for improved protection against pneumococcal disease in adults, Pfizer seeks the following indication:

> "PREVNAR 13 is indicated for the active immunization for the prevention of pneumococcal disease (including pneumonia and invasive disease) caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults age 50 years and older."

At the time of initial approval, the following statement will be included in the Indications section of the package insert.

> "This indication is based on immune response elicited by PREVNAR 13, and there have been no controlled trials in adults demonstrating a decrease in invasive pneumococcal disease or pneumococcal pneumonia after vaccination with PREVNAR 13."

This statement will be removed only following successful completion, submission, and FDA approval of the confirmatory pneumonia trial. If the trial is not successful, the FDA will consider whether there is adequate evidence of clinical benefit to support an indication not including pneumonia.

When 13vPnC is introduced in the market for use in adults 50 years and over, the target population will be made up of 2 distinct groups.

- Adults who have not received the 23vPS vaccine (23vPS-naïve subjects), and
- Adults who have previously been vaccinated with the 23vPS vaccine (23vPS-preimmunized subjects).

These groups were evaluated separately in clinical trials because their immune status was expected to have an impact on subsequent vaccination with any vaccine. This effect was not only demonstrated to be true in the phase 3 trials included in the supplemental BLA, but was

also critical for appropriate vaccination planning for long-term protection, as described elsewhere in the briefing document.

3.0 CLINICAL PROGRAM

3.1 OPA Antibody Responses as the Basis of Comparison

Since its discovery, the serotype-specific polysaccharide capsule of the pneumococcus has been shown to be fundamental to pathogenesis and development of protective immunity in the exposed human host. The pneumococcal polysaccharide capsule is an important virulence factor. It inhibits phagocytosis by interfering with immune recognition of cell wall constituents by complement or antibody and interferes with intracellular killing.[144] Pneumococci that lack a polysaccharide capsule are typically avirulent because of an inability to resist innate immunity.

Functional opsonophagocytic serotype-specific antibody to pneumococcal polysaccharide capsule, when combined with complement, is well established as a mediator of protection against pneumococcal disease. Since its discovery, the serotype-specific polysaccharide capsule of the pneumococcus has been shown to be fundamental to pathogenesis and development of protective immunity in the exposed human host. Studies linking the capsule to protective immunity were first advanced in the 1880s, when Felix and Georg Klemperer demonstrated that crude heat-killed pneumococci or pneumococcal extracts could protect rabbits against challenge with pneumococci, and that serum passively transferred from immunized rabbits and recovering pneumonia patients could protect naïve rabbits.[11] The ability of immune sera to induce clumping of organisms was reported by Metchnikoff,[145] and these observations led to Neufeld's development of the Quellung or capsular swelling test.[146] By 1926, Felton and Bailey demonstrated that antibody to the polysaccharide purified from the pneumococcal capsule was responsible for protection against pneumococcal infection.[147] By 1933 Ward and Enders conclusively demonstrated that antibody plus a heat-inactivated substance (complement) was required to opsonize pneumococci, followed by phagocytosis by inflammatory cells.[148]

This serotype-specific antibody-mediated opsonophagocytosis is fundamental to antibody-mediated protection against pneumococci. Assays to measure this opsonophagocytic activity

(OPA) provide the best laboratory measure of vaccine-induced protection in humans.[14] Data from the 7vPnC and 13vPnC clinical programs demonstrated a noted correspondence between capsular anti-polysaccharide IgG and anti-bacterial OPA responses. Both immune responses elicited by 13vPnC in the pediatric program were measured and, generally (depending on the serotype), the anti-polysaccharide responses mirrored the functional antibody activity. A protective threshold of OPA response has been proposed for prevention of IPD in children.[149] A protective threshold of OPA response has not been defined for adults. However, given the overwhelming evidence that OPA response is the basis for protection, and that 23vPS induces OPA and provides some measure of protection against pneumococcal disease in adults, it is reasonable to advance non-inferiority of 13vPnC OPA response to that of 23vPS based on comparison of OPA GMTs and proportion of responders above the OPA lower limit of quantitation (LLOQ), as sufficient to support the adult indication.

Functional anti-bacterial OPA antibody responses, as quantitatively measured by validated assays, have long been considered the immunological basis for protective immunity against pneumococcal disease. Accordingly, the primary objectives of the adult program pivotal trials are based on the comparison of the OPA responses elicited by 13vPnC compared to those elicited by 23vPS with evaluation of the anti-polysaccharide IgG responses as secondary outcomes.

The very large numbers of OPA assays required to support the adult program led to a redevelopment and automation of the OPA assay method for each of the 13 serotypes. The OPA assay is not standardized to a common external standard; hence, the vaccine response comparisons are only valid within each serotype and, preferably, between study groups within the same clinical study. The quantitative response values cannot be compared across different serotype assays.

3.2 Clinical Trial Endpoints and Comparisons

As discussed with the US and EU agencies, the 13vPnC functional OPA antibody responses were to be compared to the 23vPS responses for each of the 12 serotypes in common to both vaccines, and the non-inferiority of the responses were to be demonstrated. The response to

the additional serotype 6A, which is contained in 13vPnC but not in 23vPS, was to be assessed by demonstration of a 4-fold increase in the specific OPA titer above preimmunization levels. As 23vPS does elicit a certain amount of anti-type 6A antibody (as a result of immunological cross-reactivity with serotype 6B in the vaccine), the comparisons between the 2 vaccines were formally established to show a statistically significantly greater response in the 13vPnC vaccine compared to 23vPS. (Serotype 6A in the vaccine is also likely to provide immune response against emerging serotype 6C that is not provided by 6B in 23vPS vaccine, based on cross-reactivity of anti-6A sera that is not observed with anti-6B sera).[150]

Non-inferiority is defined as the lower limit of the 95% CI for the GMT ratio >0.5, or lower limit of the 95% CI for the difference in proportion achieving LLOQ is >-10%. "Superiority" (statistically significantly greater) is defined as the lower limit of the 95% CI for the GMT ratio is >1.0 (>2.0 for serotype 6A, not contained in 23vPs), or lower limit of the 95% CI for the difference in the proportion of subjects achieving LLOQ is >0%.

3.3 Summary of 13vPnC Adult Program Key Results

The 13vPnC clinical development program consisted of six 13vPnC phase 3 trials, two 13vPnC phase 2 trials, and one precursor 7vPnC trial. The 7vPnC 508 trial and the 13vPnC 500 trial primarily provided data supporting the 13vPnC dosage and formulation for adults. Trial 3009 was an extension of the 500 study to a second year and provided supporting data regarding the sequential use of 13vPnC and 23vPS.

Of the phase 3 trials, studies 004 and 3005 provided the pivotal data comparing 13vPnC responses to those elicited by 23vPS after a single dose, and studies 3005 and 3010 assessed the sequencing of 13vPnC and 23vPS and the potential for establishment of memory and revaccination to maintain immunity over an extended period. The 004 study extension evaluated the sequences 13vPnC/13vPnC and 13vPnC/23vPS and 23vPS/23vPS separated by a 3.5 to 4-year interval to provide additional information on the relationship of immune memory response and revaccination response to vaccination interval and vaccine sequence. Two (2) additional phase 3 trials, 3001 and 3008, studied the coadministration of 13vPnC with the trivalent inactivated influenza vaccine (TIV). Finally, a safety trial (study 3000) in

adults previously immunized with 23vPS was performed to increase the size of the safety database in this population.

All primary immunogenicity objectives of the phase 3 trials were achieved as required for licensure. The majority of the secondary objectives were also achieved. In addition, there were no clinically meaningful differences in the safety outcomes between 13vPnC and 23vPS, although some of the revaccination sequences yielded a higher rate and severity of local reactogenicity, all of which resolved.

The following pivotal immunogenicity objectives were achieved:

- Study 004 – Demonstrated that the OPA responses to 13vPnC were non-inferior or, for most serotypes, better than the OPA responses to 23vPS in pneumococcal vaccine-naïve subjects aged 60 to 64 years. Eight serotypes in common and 6A (not contained in 23vPS) exhibited a statistically significantly greater immune response in 13vPnC recipients. In addition, the 13vPnC responses in 50 to 59-year-olds were non-inferior to the 13vPnC responses in 60 to 64-year-olds for all serotypes.
- Study 3005 – Demonstrated in adults 70 years of age or older that the OPA antibody responses to the 12 common serotypes elicited by 13vPnC were non-inferior to those elicited by 23vPS when the vaccines were administered a minimum of 5 years after a recommended dose of 23vPS. In addition, 11 of 13 serotypes (including serotype 6A) in the 13vPnC recipients elicited statistically significantly greater immune responses. Revaccination with 13vPnC a year following the initial administration of 13vPnC resulted in the maintenance of the immune response, indicating the potential to maintain protection comparable to that after the first 13vPnC dose, in 23vPS-preimmunized adults. By contrast, a study dose of 23vPS followed by a study dose of 13vPnC resulted in lower antibody responses than those observed after the initial study dose of 23vPS vaccine.
- Study 3010 – Demonstrated that the initial administration 13vPnC does not interfere with and generally improves immune response to a subsequent dose of 23vPS one year later (ie, 13vPnC at year 0 and 23vPS at year 1 or 13vPnC/23vPS), in pneumococcal vaccine-naïve individuals 60 to 64 years of age. The immune

responses following the subsequent 23vPS administration in year 1 were non-inferior, and for 6 serotypes statistically greater, than the responses observed after a single administration of 23vPS (ie, 13vPnC/23vPS vs 23vPS). The study also demonstrated that responses following an immunization sequence of 13vPnC/23vPS were non-inferior and, for 11 serotypes, statistically greater than the sequence of 23vPS/13vPnC. Follow-on administration of 13vPnC in immunization-naïve 60 to 64-year-old adults, 1 year after the initial dose of 13vPnC (ie, 13vPnC/13vPnC), resulted in a generally lower response than seen after the first dose; however 13vPnC/13vPnC induced higher antibody responses than 23vPS/13vPnC, indicating that the lower response induced by 23vPS/13vPnC was fundamentally different. In addition it was noted that although responses to 13vPnC/23vPS were generally higher than those after 23vPS, responses were generally lower after 13vPnC/23vPS than after the first dose of 13vPnC. It was hypothesized that a longer interval between doses for a 13vPnC/13vPnC regimen and 13vPnC/23vPS might be associated with improved response.

- Study 004 extension – In light of the study 3010 findings, an extension of the 004 study investigated a 3.5 to 4-year interval between doses for additional evidence of memory response and improved response after the 13vPnC/13vPnC sequence compared to 13vPnC alone. In addition this study evaluated 13vPnC/13vPnC and 13vPnC/23vPS in comparison to 23vPS/23vPS. These investigations revealed the following results: Antibody responses after 13vPnC/13vPnC were comparable or statistically higher than responses after the first dose of 13vPnC, indicating establishment of memory that permitted boosting of conjugate vaccine response after a sufficient interval (at least 3.5 years) between doses. 13vPnC/23vPS demonstrated responses to common serotypes that were generally higher than those after 23vPS, recapitulating for even more serotypes results seen in study 3010, and confirming establishment of immunologic memory to polysaccharides in common. In addition, 13vPnC/23vPS generally achieved responses that were comparable or statistically higher than those achieved by the 13vPnC alone. Hence, the interval between doses was confirmed to be important in maximizing response to either 23vPS or 13vPnC after an initial dose. In contrast, 23vPS/23vPS was associated with statistically significantly lower responses to the second dose of 23vPS confirming lack of

establishment of memory after the first dose. 13vPnC/13vPnC and 13vPnC/23vPS induced statistically significantly greater responses than the sequence 23vPS/23vPS. These data confirm that it is possible to reimmunize individuals who have received 13vPnC with a second dose of 13vPnC and thereby maintain or increase antibody levels likely to optimize protection not achievable with sequential 23vPS/23vPS. Further data to define the appropriate interval for revaccination will be part of a subsequent submission.

For all studies for which it was examined, the immune response to serotype 6A (unique to 13vPnC, not in 23vPS) elicited by 13vPnC was significantly higher than that elicited by 23vPS. The potential for greater protection against type 6A pneumococcal disease engendered by 13vPnC is noteworthy given the epidemiological importance of this serotype.

In addition to data supporting the immunologic benefits of 13vPnC, there were no clinically meaningful differences in the safety outcomes between 13vPnC and 23vPS, although some of the 13vPnC/23vPS sequence in naïve adults, and 23vPS administration to 23vPS-preimmunized adults yielded a higher rate and severity of local reactogenicity, all of which resolved.

3.4 Implications for Use of 13vPnC in Adults

The data from the clinical trials satisfy licensing criteria for indications in pneumococcal vaccine-naïve and 23vPS-preimmunized adults ≥50 years of age support the following perspectives on the use of 13vPnC in this population:

- 13vPnC vaccine elicits an improved functional (OPA) anti-pneumococcal immune response compared to 23vPS when administered to pneumococcal vaccine-naïve adults ≥50 years of age.
- 13vPnC vaccine is the preferred choice for reimmunization to enhance protection for adults who have been previously immunized with 23vPS.
- Whenever possible, 13vPnC should be administered first to pneumococcal vaccine-naïve adults ≥50 years of age to take full advantage of the immunologic benefit afforded by the conjugate vaccine. These benefits include establishment of

immunological memory and the potential for revaccination to maintain optimum immune response.

- In contrast, prior immunization with 23vPS blunts the response to a subsequent dose of 13vPnC similar to the blunting that has been historically seen with second doses of 23vPS.[56]

In additional phase 3 studies, 3001 and 3008, the coadministration of 13vPnC with the trivalent inactivated influenza vaccine (TIV) was studied.

- Study 3001 and 3008 - TIV antibody responses were non-inferior for all 3 antigens when coadministered with 13vPnC vaccine in 50 to 59-year-old adults, compared to administration of TIV alone. In ≥65-year-old adults, the 95% lower confidence interval (CI) for the difference, between vaccine groups (13vPnC+TIV vs TIV alone), in proportion of subjects with a ≥4-fold antibody response to H3N2 was slightly below (-10.4%) the predefined non-inferiority 95% lower CI of -10%. However, the proportion of subjects with HAI titers >40 associated with protection was high (96.5%) and within 1% of values in subjects who received TIV alone (97.4%). Responses to H1N1 and B antigens in ≥65-year-old adults were non-inferior after concomitant 13vPnC and TIV compared to TIV alone.

  Serotype-specific anti-polysaccharide IgG immune responses to 13vPnC coadministered with TIV were non-inferior to those of 13vPnC administered alone, based on a predefined lower 95% CI of the GMT ratio >0.5, with the exception of serotype 19F in adults ≥65 years of age. However, IgG responses were statistically lower (upper 95% CI of GMT ratio <1) for 8 of 13 serotypes in adults 50 to 59 years of age, and for 6 of 13 serotypes in adults ≥65 years of age after administration of concomitant 13vPnC and TIV compared to 13vPnC alone. As a result, post-hoc opsonophagocytic activity (OPA) analyses were undertaken using the same non-inferiority criterion as for IgG responses, to further assess the immune responses to 13vPnC in these studies. The OPA responses to 13vPnC coadministered with TIV were statistically lower (upper 95% CI of GMT ratio <1) for 10 of 13 serotypes in adults 50 to 59 years of age (and lower 95% CI of GMT ratio <0.5 for 5 of 13), and statistically lower for 1 of 13 serotypes in adults ≥65 years of age (and lower 95% CI

<0.5 for 3 of 13). Hence, in both adult populations when 13vPnC was given concomitantly with TIV, the immune responses to 13vPnC were lower for at least some serotypes compared to when 13vPnC was given alone. Accordingly, concomitant use of 13vPnC and influenza vaccine should be dictated by clinical circumstances.

The safety profile of 13vPnC is acceptable in pneumococcal vaccine-naïve and pneumococcal vaccine-experienced adults.

- The safety and reactogenicity profile of a single dose of 13vPnC has been shown to be acceptable and comparable to 23vPS in 23vPS-naïve subjects.
- Subjects preimmunized with 23vPS showed an improved safety and reactogenicity profile after vaccination with 13vPnC compared to revaccination with 23vPS.
- A second dose of 13vPnC given at a 1-year or 3.5 to 4-year interval, is not associated with increased reactions (13vPnC/13vPnC).
- In contrast, administration of a study dose of 23vPS to adults ≥70 years of age previously immunized at least 5 years earlier with 23vPS, or administration of 13vPnC followed by 23vPS one year or 3.5 to 4 years later (13vPnC/23vPS) in younger adults showed higher local reactogenicity and an increase for some systemic reactions. Likewise, the administration of 23vPS/23vPS was generally associated with the highest rates of local and sometimes systemic reactions after the second dose. The common feature for each of these immunization regimens is receipt of 23vPS with its high pneumococcal polysaccharide load (25 µg for each polysaccharide) in a setting of pre-existing antibody from prior vaccination. This high polysaccharide load in the setting of prior antibody is likely to be responsible for the increased reactions seen. Higher pre-existing antibody titers have been associated with increased reactions after 23vPS vaccine whether present at the time of initial vaccination or at revaccination.[1]
- Subjects vaccinated with 23vPS followed 1 year later by 13vPnC (23vPS/13vPnC) also showed an acceptable safety and reactogenicity profile.
- Coadministration of 13vPnC with TIV was well tolerated although somewhat more local and systemic events were observed in the younger subjects (50 to 59 years)

compared to older subjects (≥65 years). Higher trends or statistically higher rates were seen for some systemic events, after concomitant use, but were judged to fall within a satisfactory safety profile.

In conclusion, the 13vPnC vaccine has met the requirements for licensure as agreed with both US and EU regulators. In addition, the specific requirement set forth by the FDA to demonstrate potential benefit for older adults who have previously been vaccinated with the 23vPS vaccine was met. Specifically, 13vPnC demonstrates statistically higher functional antibody responses, establishes memory, and permits revaccination to extend potential protection not achievable with 23vPS. Likewise, in pneumococcal vaccine-naïve adults, 13vPnC also demonstates statistically higher functional antibody responses, establishes memory, and permits revaccination to extend protection. These features make possible vaccination of adults beginning at 50 years of age and revaccination to maintain optimum immune response for a lifetime of risk, goals that are not possible with 23vPS. Such 13vPnC immunologic attributes should confer improved protection against pneumococcal disease, including community-acquired pneumonia, across a wider age range of adults than is currently possible with 23vPS alone. Thus, the clinical program has achieved the requirement for approval via the Accelerated Approval regulation in the US prior to completion of the confirmatory community-acquired pneumonia efficacy trial, thereby permitting the vaccine to be introduced into the public health system to satisfy an important unmet medical need for protection of adults against pneumococcal disease.

3.5 Design of Clinical Program

3.5.1 Study Populations

The clinical dossier includes eight 13vPnC trials and one precursor 7vPnC trial in adults. The clinical development program investigated the use of 13vPnC in adults over 50 years of age in 2 target groups with the following age stratifications:

1. Individuals naïve to 23vPS:
   - ≥65 years
   - 60 to 64 years
   - 50 to 59 years
2. Individuals preimmunized with 23vPS:
   - ≥68 years

Each trial included healthy adults and immunocompetent subjects with stable underlying conditions such as cardiovascular disease, chronic pulmonary disease, renal disease, and diabetes, because it is known that these are common conditions in adults at increased risk of serious pneumococcal CAP and IPD. Subjects with pre-existing stable disease (defined as disease not requiring significant change in therapy[a] or hospitalization for worsening disease 12 weeks before receipt of study vaccine) were eligible. Descriptive information on immune responses in subsets of subjects with non-immunocompromising medical conditions is provided in the dossier for each trial. Trials excluded immunocompromised individuals from enrollment and evaluable immunogenicity analysis, since immune response to conjugated vaccine and potential for protection in these populations are uncertain. Excluded subjects consisted of immunocompromised persons who had known or suspected immunodeficiency or who received treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids (eg, for cancer, HIV infection, or autoimmune disease). If systemic corticosteroids had been administered short term for treatment of an acute illness, subjects were to be excluded from the study until corticosteroid therapy had been discontinued for at least 30 days. Also excluded were subjects with serious chronic disorders (including metastatic malignancy, severe chronic obstructive pulmonary disease) requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that in the investigator's opinion precluded the subject from participating in the study. Demographics of the risk conditions in the population under study are shown in Table 3-1.

[a] Change in dose or therapy within a category (eg, change from 1 nonsteroidal anti-inflammatory drug [NSAID] to another) was allowed. Change to new therapy categories (eg, surgery or addition of a new pharmacologic class) was allowed only if it was not caused by worsening disease. A change to new therapy categories caused by worsening disease was considered significant.

Table 3-1: Number of Adults with Chronic Medical Conditions Who Received 13vPnC at Vaccination 1 (Year 0) in the Six Phase 3 Studies

Number and Percentage of 13vPnC Recipients with Chronic Medical Conditions		
Chronic pulmonary diseases	790	16%
Diabetes mellitus	700	14%
Cardiovascular diseases	575	11%
Renal and urinary disorders	100	2%
Chronic liver disease including alcoholic liver disease and alcoholism	30	1%
Percentage of 13vPnC Recipients Across Studies with One or More Chronic Medical Conditions		
In adults ≥65 years of age	37-56%	
In adults 50-64 years of age	17-26%	
Number of 13vPnC Recipients with a Smoking History		
Any smoking history	1790	46%
Smoking in the last 6 months	385	11%

3.5.2 13vPnC Trials

Two (2) pivotal non-inferiority trials were conducted in which 13vPnC response was compared to the 23vPS immune response, 1 in naïve subjects 50 to 64 years of age (study 004), and 1 in 23vPS-preimmunized subjects ≥70 years of age (study 3005). The primary goal of these studies was to support 13vPnC licensure in both 23vPS-naïve and 23vPS-preimmunized populations. A third phase 2 non-inferiority trial comparing 13vPnC and 23vPS in naïve subjects ≥65 years of age provides supportive data (study 500). The 500 study used a formulation that contained the same concentrations of conjugated serotypes but did not include 0.02% polysorbate 80 contained in the final 13vPnC formulation and included a comparison of 13vPnC with and without $AlPO_4$.

The phase 2 study 500 and its 3009 follow-on study also provide supportive data regarding sequential use of pneumococcal vaccine. (Results of these supportive studies are not included in this briefing document.)

Study 3010 was designed to evaluate sequential administration of 13vPnC and 23vPS spaced 1 year apart in 23vPS-naïve subjects 60 to 64 years of age. The primary goal of this study was to support the hypothesis that whenever possible, 13vPnC should be given as the first pneumococcal vaccine. An extension of the 004 study evaluated the relationship between a 3.5 to 4-year dosing interval and antibody response with successive administration of 13vPnC or 23vPS vaccines.

It is recognized that coadministration of the influenza vaccine and pneumococcal vaccine may be desirable in some circumstances from a convenience and public health perspective. Studies 3001 (adults 50 to 59 years of age) and 3008 (adults ≥65 years of age) were conducted in the US and EU, respectively, to evaluate the compatibility of 13vPnC given concomitantly with influenza vaccine.

Safety and tolerability data were collected in all clinical trials. As shown in Section 5.0, a total of 5667 subjects vaccinated with 13vPnC were evaluated with respect to safety. Of these subjects, 3751 were 23vPS-naïve; 1916 were 23vPS-preimmunized. A total of 1128 23vPS-naïve subjects received 13vPnC concomitantly with influenza vaccine. In addition to the safety assessment performed in study 3005, a large scale safety trial, study 3000, was performed in 1049 subjects vaccinated with 1 dose of 13vPnC at least 3 years after 1 or more nonstudy doses of 23vPS. The tolerability and safety information arising from the formulation study 500 (and follow-on study 3009), are considered as supportive data. In 3 primary trials (studies 3000, 3005, 3008) 3911 subjects received 13vPnC as an initial study vaccination. Of those, 1168 (29.9%) were 65 to 74 years of age, while 902 (23.1%) were 75 years of age and older.

The precursor trial 6097A1-508 was performed with the 7vPnC vaccine to evaluate the potential of pneumococcal conjugate vaccine to add value to a comprehensive approach to prevention of pneumococcal disease. Experience was instructive in designing the 13vPnC

clinical program. In addition, this 7vPnC study explored the relationship of immune response and safety profile to vaccine dosage. Based on results of the 508 study, the standard 0.5-mL dose licensed for use in children was chosen for investigation in the adult 13vPnC program.

4.0 OVERVIEW OF IMMUNOGENICITY OBJECTIVES AND RESULTS

This section provides a summary description of immunogenicity objectives and results for each trial. For each study, 2 immunogenicity analysis populations were defined: the evaluable immunogenicity population (which was considered the primary population) and the all-available immunogenicity population. Results in this section are provided for the evaluable immunogenicity population only, as the study conclusions do not differ when considering the results from the all-available immunogenicity populations. The data for the latter are provided in the individual CSRs.

4.1 Analysis of Immunogenicity by OPA

Statistical criteria are described in association with each of the study objectives provided later in this section. In brief, the primary endpoints for the 12 serotypes common to 13vPnC and 23vPS in phase 3 studies were serotype-specific OPA responses. Non-inferiority comparisons between experimental groups of serotype-specific OPA geometric mean titers (GMTs) measured 1 month after vaccination were performed to meet key objectives for the 004, 3005, and 3010 trials. Non-inferiority for selected predefined comparisons was declared if the lower bound of the 2-sided, 95% confidence interval (CI) for the ratio of the GMTs (GMR) was greater than 0.5 (2-fold criterion). Statistically significantly greater responses were declared if the lower bound of the 2-sided 95% CI for the GMR was greater than 1. In studies where subjects received 2 successive doses of 13vPnC, geometric mean fold rises (GMFR) were calculated based on GMTs obtained one month after each dose. For predefined comparisons in this circumstance, the lower bound of the 2-sided, 95% CI for the GMFR was >0.5 (2-fold criterion) was used. Results were also provided for these comparisons for circumstances in which the GMFR was statistically lower (upper bound of the 2-sided 95% CI was <1) or statistically higher (lower bound of the 2-sided 95% CI was >1).

For each of the 12 common serotypes and 6A, key prespecified analyses for some studies compared the proportion of subjects achieving an OPA titer ≥ lower limit of quantitation (LLOQ) measured 1 month after vaccination across experimental groups. Non-inferiority for

a given serotype was demonstrated if the lower bound of the 2-sided, 95% CI for the difference in proportions was greater than -0.10. Statistically greater response was declared if the lower bound of the 2-sided, 95% CI for the difference in proportions was greater than 0; statistically lower response was declared if the upper bound of the 2-sided, 95% CI for the difference in proportions was less than 0.

For serotype 6A in studies 004 and 3005, the primary endpoint was the proportion of subjects exhibiting a 4-fold rise in anti-6A OPA titer. For serotype 6A in studies 004 and 3005, the primary analysis compared the proportion of subjects achieving a 4-fold rise in OPA titer (from before vaccination to 1 month after vaccination) in the 13vPnC group with the proportion in the 23vPS group. Superiority of the response for 13vPnC was declared if the lower bound of the 2-sided, 95% CI for the difference in proportions (13vPnC–23vPS) was greater than 0. For serotype 6A in study 004 (secondary objective) and study 3005 (exploratory objective), objectives were designed to demonstrate that the lower bound of the 95% CI of the proportion of subjects administered 13vPnC and achieving an anti-6A OPA titer of at least the LLOQ was 85% or higher. For serotype 6A in studies 004 and 3005, secondary analyses compared the anti-6A OPA GMT measured 1 month after vaccination in the 13vPnC group with the GMT in the 23vPS group. Superiority of the response to serotype 6A in 13vPnC was declared if the lower bound of the 2-sided, 95% CI for the GMR (GMT 13vPnC/GMT 23vPS) was greater than 2 (2-fold criterion).

In some studies (004, 3001), as a supportive analysis, GMTs were also evaluated using an analysis of covariance (ANCOVA). The dependent variable was the log transformed postvaccination OPA value. The model included terms for vaccine group and baseline OPA value (ln scale), with current smoking status as a covariate. The least squares means, adjusted for the covariate, for each vaccine group and for the difference in vaccine groups (13vPnC–23vPS) was computed, along with their 2-sided, 95% CIs.

Descriptive statistics were applied as indicated by individual objectives.

4.2 Additional Immunogenicity Analyses

4.2.1 Anti-Polysaccharide IgG Concentration Comparisons

Serum IgG geometric mean concentrations (GMCs) were analyzed using procedures similar to those used for the evaluation of OPA GMTs.

4.2.2 Persistence of Antibody Response

OPA and IgG responses at the 1-year time point were assessed using descriptive statistics and graphical displays.

4.2.3 Reverse Cumulative Distribution Curves

Reverse cumulative distribution curves (RCDCs) were generated for postvaccination OPA titers and IgG concentrations.

4.2.4 Plots of Individual Subject Responses

Graphical displays of individual subject OPA responses before and after each vaccination were generated as a post-hoc analysis for studies investigating vaccination sequence, to assist in understanding sequential responses in relation to preimmunization antibody levels.

4.2.5 Immunogenicity Analysis Methods for Evaluation of Concomitant Administration of 13vPnC and TIV

For the 3 virus subtypes contained in TIV, the proportion of subjects achieving a 4-fold increase in hemagglutination inhibition assay (HAI) titers from prevaccination to 1 month after vaccination was computed by vaccine group. To assess the treatment difference (13vPnC+TIV and placebo+TIV), exact, unconditional, 2-sided 95% CIs on the difference in proportions were calculated using the non-inferiority procedure of Chan and Zhang[151] using the standardized test statistic and γ=0.000001. Non-inferiority for a given virus subtype was demonstrated if the lower limit of the 2-sided 95% CI, computed using the procedure of Chan and Zhang,[151] for the difference in proportions (13vPnC+TIV – TIV alone) was $\geq$0.10. Additional post-hoc analyses of response were performed based on guidelines for seasonal trivalent inactivated influenza vaccines from the FDA and European Medicines Agency (EMA).[152,153]

For the 13 serotypes contained in 13vPnC, the serotype-specific IgG antibody concentrations were logarithmically transformed for analysis. Within each vaccine group and for each serotype, geometric means of the antibody concentrations at all visits (prevaccination, 1 month after vaccination with TIV, and 1 month after dose 2) were calculated. Two (2)-sided 95% CIs were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. Non-inferiority was evaluated using the ratio of the postvaccination IgG antibody GMCs of 13vPnC+TIV to 13vPnC. The criterion upon which to declare non-inferiority was the lower limit of the 2-sided 95% CI for the GMC ratio (GMR) >0.5 (2-fold criterion). The fold rises in antibody concentrations from prevaccination to 1 month postvaccination were presented by geometric means and 2-sided 95% CIs, and computed using the logarithmically transformed assay results. Because compatibility of concurrent TIV and 13vPnC administration was demonstrated only if the lower limits of the 2-sided 95% CIs for all 3 influenza virus subtype comparisons were >-0.10 and all 13 pneumococcal serotype GMC ratio comparisons were >0.5, adjustment for multiplicity was not needed.

4.3 Evidence to Support a Single Dose of 13vPnC for Vaccination of Pneumococcal Vaccine-Naïve Adults or Revaccination of 23vPS-Experienced Adults to Establish or Extend Optimum Protection Against Pneumococcal Serotypes in Common

4.3.1 Immunogenicity Results of the Pivotal Non-Inferiority Study in Pneumococcal Vaccine-Naïve Adults, Study 004

Study 004 was undertaken based on the underlying premise that a pneumococcal conjugate vaccine should induce quantitatively and possibly qualitatively better immune responses than the polysaccharide vaccine in pneumococcal vaccine-naïve adults ≥50 years of age, leading to the induction of both immunological memory and to substantially enhanced protection against invasive pneumococcal disease.

Study 004 was initially planned to compare the immunogenicity, tolerability, and safety of 13vPnC and 23vPS in adults 60 to 64 years of age who were naïve to 23vPS, using a randomized, modified double-blind design. Subsequently, the protocol was amended to add a cohort of subjects 50 to 59 years of age (cohort 2), and a cohort of subjects 18 to 49 years of age (cohort 3). Both of these groups received open-label 13vPnC. The addition of these

cohorts served to bridge and assess the immune response to 13vPnC in these age groups and to compare these responses with the responses of cohort 1 (subjects 60 to 64 years of age). This submission includes data from cohort 1 and cohort 2, and supports an indication for 13vPnC administration in pneumococcal vaccine-naïve adults ≥50 years of age. Data from cohort 3 are not part of this submission, and will be submitted at a later date to support a 13vPnC indication in pneumococcal vaccine-naïve adults less than 50 years of age.

The study design is shown in Figure 4-1.

Figure 4-1: Study 004 Design

Study Design			
Age	**Cohort**	**N**	**Year 0**
60-64 yo Naive	**1.1**	**370**	**13vPnC**
	1.2	**370**	**23vPS**
50-59 yo Naive	**2**	**370**	**13vPnC**

This study met all primary and secondary objectives for cohort 1 (adults 60 to 64 years of age) and cohort 2 (adults 50 to 59 years of age).

4.3.1.1 Key Immunogenicity Objectives and Results, Cohort 1, Adults 60 to 64 Years of Age, Study 004

13vPnC is as immunogenic as 23vPS for the 12 common serotypes contained in 13vPnC as measured by serotype-specific OPA titers 1 month after vaccination (1st of 2 coprimary objectives). OPA response after 13vPnC vaccine was non-inferior to the response after 23vPS for the 12 serotypes in common when administered to pneumococcal vaccine-naïve adults 60 to 64 years of age (Table 4-1).

The proportion of subjects receiving 13vPnC and exhibiting a 4-fold increase in the 6A OPA titer is statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting the same 4-fold increase (2nd of 2 coprimary objectives) (Table 4-2).

13vPnC is statistically significantly more immunogenic than 23vPS for at least some of the 13 serotypes contained in 13vPnC as measured by serotype-specific OPA titers 1 month after vaccination (secondary objective) (Table 4-1, shaded cells)**.** For the evaluable immunogenicity population, the lower limit of the 2-sided, 95% CI for the GMR (13vPnC GMT/23vPS GMT) was >1 for 8 of the 12 common serotypes.

The anti-6A OPA titer in the 13vPnC recipients is statistically significantly greater than the anti-6A titer in 23vPS recipients measured 1 month after vaccination. That is, the lower limit of the 95% CI of the geometric mean ratio (GMT 13vPnC/GMT23vPS) was greater than 2-fold (secondary objective) (Table 4-1, shaded row for 6A)**.**

The lower bound of the 95% CI on the proportion of subjects administered 13vPnC and achieving an anti-6A OPA titer of at least the lower limit of quantitation (LLOQ) is 85% or higher (secondary objective). The lower bound of the 95% CI for the proportion of 13vPnC recipients achieving an anti-6A OPA titer ≥LLOQ was 93.3%.

Table 4-1: Study 004 – Naïve Subjects 60-64 yo, OPA GMTs After Dose 1 13vPnC vs 23vPS

Serotype	13vPnC GMT	23vPS GMT	GMT Ratio	(95% CI)
1	146	104	1.4	(1.10, 1.78)
3	93	85	1.1	(0.90, 1.32)
4	2062	1295	1.6	(1.19, 2.13)
5	199	162	1.2	(0.93, 1.62)
6B	1984	788	2.5	(1.82, 3.48)
7F	1120	405	2.8	(1.98, 3.87)
9V	1164	407	2.9	(2.00, 4.08)
14	612	692	0.9	(0.64, 1.21)
18C	1726	925	1.9	(1.39, 2.51)
19A	682	352	1.9	(1.56, 2.41)
19F	517	539	1.0	(0.72, 1.28)
23F	375	72	5.2	(3.67, 7.33)
6A	2593	213	12.1	(8.63, 17.08)

- Non-inferiority criterion met for all serotypes
- Response to 9 of 13 serotypes statistically significantly greater for 13vPnC vs 23vPS

Table 4-2: Study 004 – Naïve Subjects 60-64 yo, ≥4-Fold Increase in 6A OPA Titer 13vPnC vs 23vPS

Serotype	13vPnC %	23vPS %	Difference	(95% CI)
6A	88.5	49.3	39.2	(33.0, 45.1)

- **Proportion of 13vPnC subjects with 4-fold increase in 6A titer was superior to 23vPS**

4.3.1.2 Summary of Additional Objectives and Results, Cohort 1, Adults 60 to 64 Years of Age, Study 004

The proportion of subjects achieving an OPA titer ≥LLOQ to the 12 common serotypes contained in 13vPnC in response to 13vPnC was non-inferior to the proportion of subjects achieving an OPA titer ≥LLOQ in response to 23vPS measured 1 month after vaccination for all 12 common serotypes (secondary objective). This secondary non-inferiority objective was met for all of the 12 common serotypes, and responder rates were statistically superior for 7 of the 12 common serotypes (1, 6B, 7F, 9V, 18C,19A, 23F).

The proportion of subjects receiving 13vPnC and exhibiting a positive anti-6A OPA response at the LLOQ is statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting the same response (exploratory objective).

13vPnC was as immunogenic as 23vPS for the 12 common serotypes contained in 13vPnC as measured by serotype-specific immunoglobulin G (IgG) antibody concentrations obtained from serum collected 1 month after vaccination in a subset of 100 subjects (exploratory objective). This objective was met for all serotypes except serotype 14 (GMR 0.73, 95% CI: 0.46, 1.16).

Persistence of antibody by IgG and OPA was assessed in a subset of subjects 1 year after vaccination (exploratory objective). OPA GMTs for all serotypes in both vaccine groups were generally lower at 1 year after vaccination than at 1 month after vaccination, but higher at 1 year after vaccination than at prevaccination. For the 8 common serotypes for which OPA titers were statistically significantly greater at 1 month after 13vPnC compared to 23vPS, point estimates of titers remained higher in the 13vPnC group compared with the 23vPS group at 1 year (overlapping 95% CIs) for serotypes 1, 4, 6B, 7F, 18C, and 23F; there was no apparent separation in titers for serotypes 9V and 19A. IgG responses revealed similar results.

4.3.1.3 Key Immunogenicity Objective, Cohort 2, Ages 50 to 59 Years, Study 004

The immune response to the 13 serotypes in 13vPnC in the 50 to 59-year-old age group is non-inferior to the immune response to 13vPnC in the 60 to 64-year-old age group as

measured by serotype-specific OPA titers 1 month after vaccination (primary objective in 50 to 59-year-old age group). For the evaluable immunogenicity population, the primary objective non-inferiority criterion was met for all 13 serotypes for cohort 2 (adults 50 to 59 years of age); that is, the lower limit of the 2-sided, 95% CI for the OPA GMR (cohort 2 GMT/cohort 1 GMT) was >0.5 (2-fold criterion) for each of the 13 serotypes (Table 4-3). The protocol and SAP did not prespecify an analysis to demonstrate superiority of the immune response among subjects in cohort 2 relative to the immune response in subjects receiving 13vPnC in cohort 1. However, using the same criterion that was used for the demonstration of superiority of 13vPnC relative to 23vPS in cohort 1 (lower limit of the 2-sided, 95% CI for the GMR >1), the immune response 1 month after vaccination in cohort 2 was statistically significantly higher than the response among subjects receiving 13vPnC in cohort 1 for 9 serotypes.

Table 4-3: Study 004 – Naïve Subjects, OPA GMTs After 1 Dose of 13vPnC 50-59 yo vs 60-64 yo

Serotype	13vPnC in 50-59 yo GMT	13vPnC in 60-64 yo GMT	GMT Ratio	(95% CI)
1	200	146	1.4	(1.08, 1.73)
3	91	93	1.0	(0.81, 1.19)
4	2833	2062	1.4	(1.07, 1.77)
5	269	199	1.4	(1.01, 1.80)
6A	4328	2593	1.7	(1.30, 2.15)
6B	3212	1984	1.6	(1.24, 2.12)
7F	1520	1120	1.4	(1.03, 1.79)
9V	1726	1164	1.5	(1.11, 1.98)
14	957	612	1.6	(1.16, 2.12)
18C	1939	1726	1.1	(0.86, 1.47)
19A	956	682	1.4	(1.16, 1.69)
19F	599	517	1.2	(0.87, 1.54)
23F	494	375	1.3	(0.94, 1.84)

- Non-inferiority met for all serotypes
- Response to 9 of 13 serotypes statistically significantly greater for 50-59 yo vs 60-64 yo

4.3.1.4 Additional Immunogenicity Objectives, Cohort 2, Adults 50 to 59 Years of Age, Study 004

For each of the 13 serotypes in 13vPnC, the proportion of subjects achieving a serotype-specific OPA titer ≥LLOQ in the 50 to 59-year-old age group (cohort 2) is non-inferior to the proportion of subjects achieving an OPA titer ≥LLOQ in the 60 to 64-year-old age group (cohort 1) measured 1 month after vaccination (secondary objective). This objective was met for all 13 serotypes.

13vPnC in the 50 to 59-year-old age group is as immunogenic as 13vPnC in the 60 to 64-year-old age group as measured by serotype-specific IgG concentrations obtained 1 month after vaccination in a subset of 100 subjects (exploratory objective). This criterion was satisfied and, although not prespecified, the immune response to 13vPnC in cohort 2 was significantly greater than the response to 13vPnC in cohort 1 for 7 serotypes: 4, 5, 6A, 6B, 14, 19A, and 19F.

Persistence of antibody in the 50 to 59-year-old age group by IgG and OPA was assessed in a subset of subjects 1 year after vaccination (exploratory objective). Point estimates for 1 year OPA values were higher for all serotypes in cohort 2 compared to cohort 1, (non-overlapping 95% CIs for 4, 6B, 9V, 14, 19A), except for serotype 3 for which curves showed little separation. IgG antibody responses were similar.

Reverse cumulative distribution curves (RCDCs) support higher antibody responses after 13vPnC compared to 23vPS in pneumococcal vaccine-naïve adults 50 to 64 years of age (Figure 4-2 to Figure 4-5).

An OPA threshold of 1:8 has been proposed as a correlate for protection for the pediatric population,[149,154,155] but a threshold of protection, based on a proportion of responders at or above a given OPA titer, has not been defined for adults. However, the RCDC curves, showing proportion of responders for a given titer, provide convincing reassurance that whatever threshold or OPA response is associated with protection, the proportion of responders after 13vPnC administration is equivalent or higher than the proportion of responders after 23vPS administration.

RCDCs from study 6115A1-004 (Figure 4-2 to Figure 4-5) show OPA responses after 13vPnC in 60 to 64 year olds (cohort 1) and 50 to 59 year olds (cohort 2) in comparison to 23vPS responses in 60 to 64 year olds (cohort 1). Note that for both 13vPnC age cohorts, point estimates of the proportion of responders for a particular OPA titer to serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 18C, 19A, and 23F are higher than those after 23vPS over the entire range of measurable titers. For serotypes 3 and 19F, the curves are superimposed over the full range of titers, and for serotype 14, the curve is superimposable up to a titer of at least 1:500. IgG responses are consistent with these findings. So, given that OPA is the acknowledged immunologic measure of protection, it is reasonable to conclude that 13vPnC will demonstrate overall efficacy at least non-inferior for all and superior for most serotypes in common, compared to the observed efficacy of 23vPS. A defined threshold of protection is not required to reach such a conclusion. Hence whether based on non-inferiority comparisons of OPA GMTs, or proportion of responders for any given titer, 13vPnC is likely to provide superior protection to that of 23vPS for most serotypes in common, and at least equivalent protection for the remainder, in pneumococcal vaccine-naïve adults.

Figure 4-2: Study 004 – Naïve Subjects, OPA RCDCs 1 Month After 13vPnC or 23vPS, Serotypes 1, 3, 4, 5

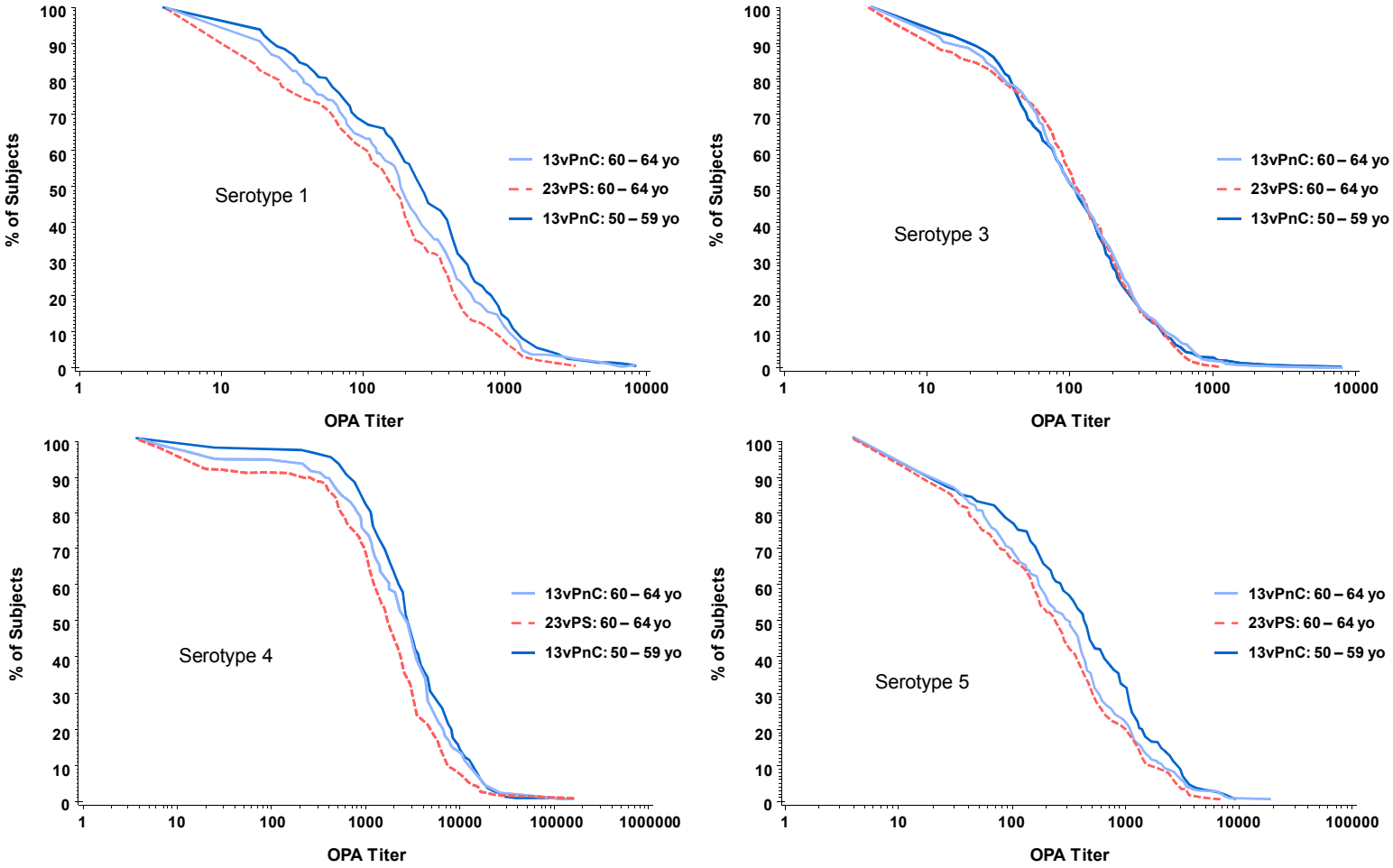


Figure 4-3: Study 004 – Naïve Subjects, OPA RCDCs 1 Month After 13vPnC or 23vPS, Serotypes 6A, 6B, 7F, 9V

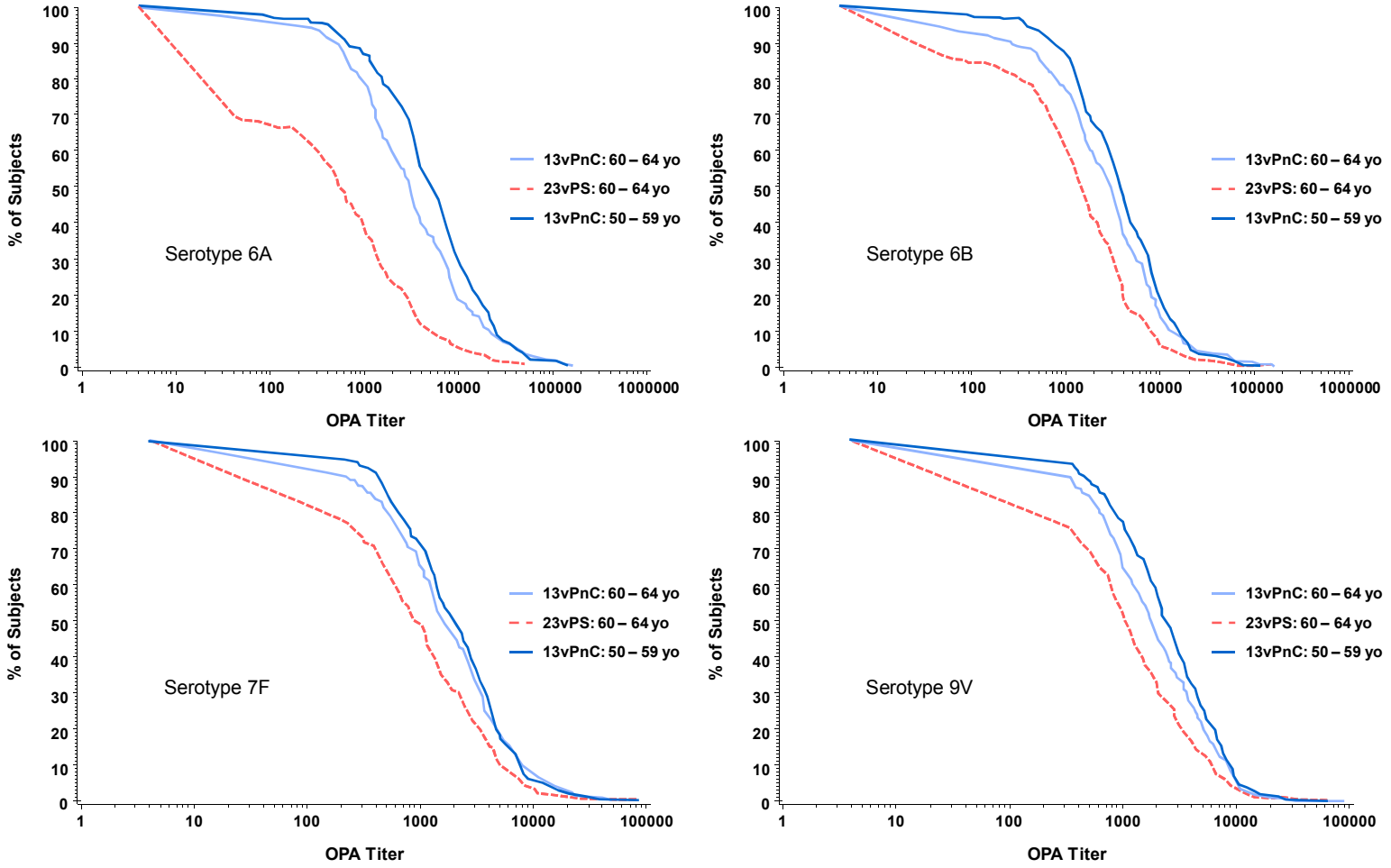


Figure 4-4: Study 004 – Naïve Subjects, OPA RCDCs 1 Month After 13vPnC or 23vPS, Serotypes 14, 18C, 19A, 19F

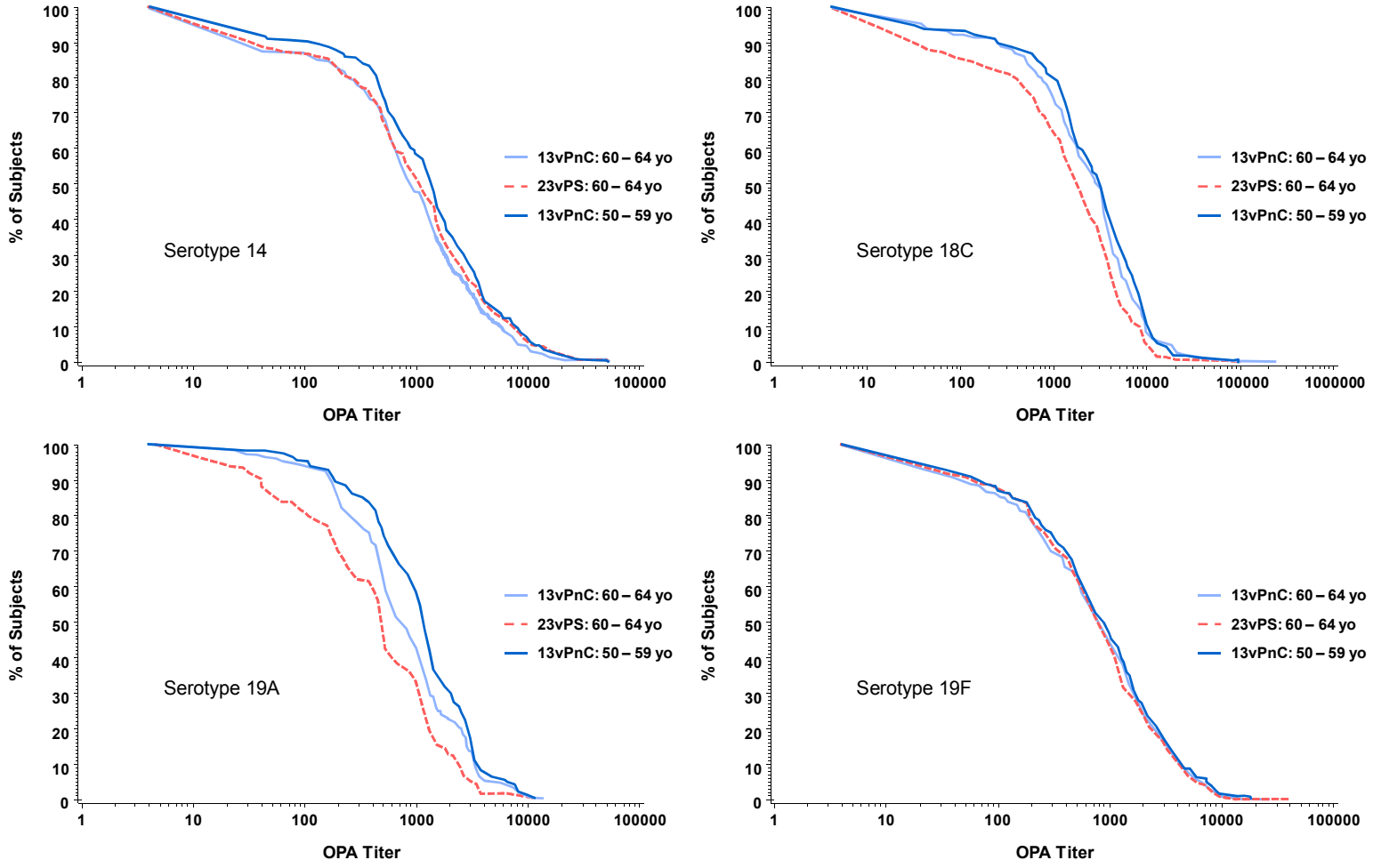
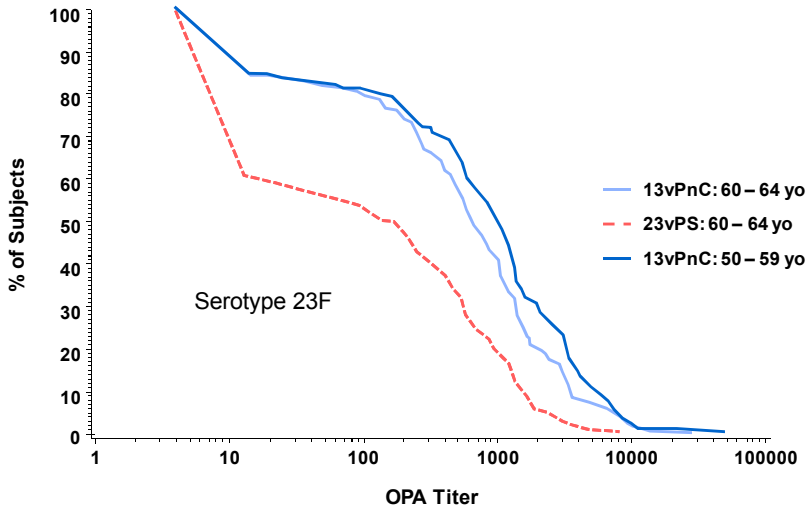


Figure 4-5: Study 004 – Naïve Subjects, OPA RCDCs 1 Month After 13vPnC or 23vPS, Serotype 23F



4.3.1.5 Overall Immunogenicity Conclusions in Pneumococcal Vaccine Naïve Adults ≥ 50 Years of Age, Study 004

All primary and secondary objectives were achieved for 60 to 64-year-old and 50 to 59-year-old subjects enrolled in this study. In 60 to 64-year-old adults who were naïve to 23vPS at study entry, 13vPnC was at least as immunogenic as 23vPS for all 12 common serotypes and statistically significantly more immunogenic than 23vPS for the majority of serotypes. 13vPnC was at least as immunogenic for all serotypes and statistically significantly more immunogenic for the majority of serotypes in adults 50 to 59 years of age compared to adults 60 to 64 years of age. Antibody levels at 1 month and 1 year after vaccination were consistently higher in 13vPnC recipients than antibody levels after 23vPS vaccine. These findings are consistent with greater and more durable immunogenicity after 13vPnC than 23vPS in adults 50 to 64 years of age, and also indicate an inverse immune response to 13vPnC with age. These findings support a single dose of 13vPnC for vaccination of pneumococcal vaccine-naïve adults to provide optimum protection against the serotypes most commonly associated with serious pneumococcal disease.

4.3.2 Immunogenicity Objectives and Results After a Single Study Dose of 13vPnC in Pneumococcal Vaccine-Experienced Adults ≥70 Years of Age, Study 3005

Readministration of 23vPS is associated with functional antibody responses 1 month after vaccination that are lower than those after the first 23vPS immunization.[56,108 156,157,158] In contrast, 7vPnC immunization of 23vPS-preimmunized adults has been shown to produce higher functional antibody responses for at least some serotypes compared to a second dose of 23vPS, and appears to be a better inducer of antibody responses associated with immunologic memory in some settings.[122] Therefore, it was important to determine in the 13vPnC adult clinical program, if 23vPS-preimmunized immunocompetent adults, who are in need of an effective vaccine to re-establish, maintain, and perhaps improve protection, are more likely to benefit from a dose of 13vPnC vaccine compared to a repeat dose of 23vPS.

The 3005 study evaluated the safety, tolerability, and immunogenicity data of 13vPnC administered as a 2-dose sequence over 12 months (13vPnC in year 0 and 13vPnC in year 1) compared to a 2-dose sequence of 23vPS in year 0 followed by 13vPnC in year 1 in healthy adults ≥70 years of age immunized with 23vPS at least 5 years earlier. Revaccination with 13vPnC at a 1-year interval was chosen to provide stringent conditions to detect the potential impact of either 13vPnC or 23vPS on subsequent immune response to 13vPnC administered 1 year later.

Study 3005 achieved all primary and secondary objectives for both years of the study. The design of study 3005 is shown in Figure 4-6. Results after a single dose of 13vPnC or 23vPS in year 0, will be discussed in this section.

Figure 4-6: Study 3005 Design

Study Design				
Subjects	**Group**	**N**	**Year 0**	**Year 1**
Prior PS ≥5 Years	**1**	**462**	**13vPnC**	**13vPnC**
	2	**462**	**23vPS**	**13vPnC**

4.3.2.1 Key Immunogenicity Objectives and Results After the First Study Dose of 13vPnC or 23vPS Vaccine in Year 0, Study 3005

13vPnC is as immunogenic as 23vPS for the 12 common serotypes contained in 13vPnC as measured by serotype-specific OPA titers 1 month after initial study vaccination (year 0) (1st of 2 coprimary objectives) (Table 4-4)**.** OPA response after 13vPnC was non-inferior to the response after 23vPS for the 12 serotypes in common when administered to adults ≥70 years of age who had received 23vPS at least 5 years earlier.

13vPnC is statistically significantly more immunogenic than 23vPS for at least some of the 12 common serotypes contained in 13vPnC as measured by serotype-specific OPA titers 1 month after initial study vaccination (secondary objectives) (Table 4-4, shaded). For the evaluable population, the lower limit of the 2-sided, 95% CI for the GMR (13vPnC GMT/23vPS GMT) was >1 for 10 of the 12 common serotypes: 1, 4, 5, 6B, 7F, 9V, 18C, 19A, 19F and 23F.

The anti-6A OPA titer in the 13vPnC recipients is statistically significantly greater than the anti-6A titer in 23vPS recipients measured 1 month after initial study vaccination (secondary objective) (Table 4-4, shaded)**.** For serotype 6A, the GMR (13vPnC GMT/23vPS GMT) was 9.6 (7.00, 13.26) and satisfied the criterion that the lower limit of the 2-sided, 95% CI for the GMR was >2.

Table 4-4: Study 3005 – Preimmunized Subjects ≥70 yo, OPA GMTs After Dose 1 13vPnC vs 23vPS

Serotype	13vPnC GMT	23vPS GMT	GMT Ratio	(95% CI)
1	81	55	1.5	(1.17, 1.88)
3	55	49	1.1	(0.91, 1.35)
4	545	203	2.7	(1.93, 3.74)
5	72	36	2.0	(1.55, 2.63)
6B	1261	417	3.0	(2.21, 4.13)
7F	245	160	1.5	(1.07, 2.18)
9V	181	90	2.0	(1.36, 2.97)
14	280	285	1.0	(0.73, 1.33)
18C	907	481	1.9	(1.42, 2.50)
19A	354	200	1.8	(1.43, 2.20)
19F	333	214	1.6	(1.17, 2.06)
23F	158	43	3.7	(2.69, 5.09)
6A	903	94	9.6	(7.00, 13.26)

- Non-inferiority criterion met for all serotypes
- 11 of 13 serotypes statistically significantly greater for 13vPnC vs 23vPS

The proportion of subjects receiving 13vPnC and exhibiting a 4-fold rise in the 6A OPA titer is statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting the same 4-fold rise, measured 1 month after initial study vaccination (year 0) (2nd of 2 coprimary objectives) (Table 4-5).

Table 4-5: Study 3005 – Preimmunized Subjects ≥70 yo, ≥4-Fold Increase in 6A OPA Titer 13vPnC vs 23vPS

Serotype	13vPnC %	23vPS %	Difference	(95% CI)
6A	71.1	27.3	43.8	(37.4, 49.9)

- **Proportion of 13vPnC subjects with 4-fold increase in 6A titer was superior to 23vPS**

When evaluated by age group, point estimates of 13vPnC OPA responses were consistently higher across age groups than 23vPS responses (Table 4-6).

Table 4-6: Study 3005 – Preimmunized Subjects ≥70 yo, OPA GMTs by Age

Age (Years)	Group N (range)	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
70-74	13vPnC (171 – 183)	81	55	658	68	1111	1309	316	234	311	961	407	364	192
	23vPS (173 – 197)	66	59	295	44	98	587	210	114	371	605	255	234	46
75-79	13vPnC (131 – 144)	101	67	603	92	930	1478	217	198	249	945	343	331	136
	23vPS (130 – 150)	52	44	149	36	113	397	164	103	339	534	176	201	45
≥80	13vPnC (93 – 101)	59	42	333	56	599	944	182	98	274	769	290	284	135
	23vPS (89 – 98)	41	41	156	24	65	226	89	46	134	254	147	197	35

- **Slightly lower responses in subjects ≥80 yo**
- **13vPnC responses are greater than 23vPS responses for majority of serotypes across all age groups**

4.3.2.2 Summary of Additional Objectives, Study 3005

The proportion of subjects achieving an OPA titer of at least the serotype-specific LLOQ to the 12 common serotypes contained in 13vPnC in response to 13vPnC is non-inferior to the proportion of subjects achieving an OPA titer of at least the serotype-specific LLOQ in response to 23vPS measured 1 month after initial vaccination (exploratory objective).
This objective was achieved for all 12 common serotypes, and for 9 of the 12 common serotypes (exceptions 3, 14, 19F) responses were statistically greater in 13vPnC recipients.

The lower bound of the 95% confidence interval on the proportion of subjects administered 13vPnC and achieving an anti-6A OPA titer of at least the LLOQ 1 month after initial vaccination is 85% or higher (exploratory objective) ***and***
The proportion of subjects receiving 13vPnC and exhibiting an anti-6A OPA response of at least the LLOQ is statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting the same response when measured 1 month after initial vaccination (exploratory objective).
Both of these objectives were satisfied. The 6A proportion of subjects achieving an antibody response above the LLOQ after 13vPnC was 89.8% (95% CI: 86.5%, 92.5%) and the difference in response rate (13vPnC-23vPS) was 24.7% (95% CI: 19.3%, 30.1%).

4.3.2.3 RCDC Curves Support Higher Antibody Responses After 13vPnC Compared to 23vPS in 23vPS-Experienced Adults ≥70 Years of Age

Findings in 23vPS-experienced adults permit the same conclusion regarding the clinical relevance of 13vPnC OPA responses as those after 13vPnC vaccine in pneumococcal vaccine-naïve adults. RCDC curves from study 6115A1-3005 (Figure 4-7 to Figure 4-10) show responses after a first study dose of 13vPnC in comparison to 23vPS in adults ≥70 years of age who received 23vPS at least 5 years earlier. Notably for 13vPnC recipients, point estimates of the proportion of responders for a particular OPA titer to serotypes 1, 4, 5, 6A, 6B, 9V, 18C, 19A, 19F, and 23F are higher than those after 23vPS *over the entire range of measurable titers*. For serotype 7F OPA responses are higher after 13vPnC up to an approximate titer of 1:700, then superimposable for the remaining range. For serotypes 3 and 14, OPA titers are superimposable throughout the observed range. IgG responses are consistent with these findings. So once again, given that OPA is the acknowledged immunologic basis of protection, and that responses after

13vPnC exceed 23vPS responses for most serotypes in common and are equivalent for the remainder, it is reasonable to conclude that 13vPnC will demonstrate overall efficacy that is at least non-inferior for all, and likely superior for most, serotypes in common to the observed efficacy of 23vPS. *A defined threshold of protection is not required to reach such a conclusion.* Hence, whether based on non-inferiority comparisons of OPA GMTs or proportion of responders for any given titer, 13vPnC is likely to provide superior protection to that of 23vPS for most serotypes in common, and at least equivalent protection for the remainder, in pneumococcal vaccine-experienced adults.

Figure 4-7: Study 3005 – Preimmunized Subjects ≥70 yo, OPA RCDCs 1 Month After 13vPnC or 23vPS, Serotype 1

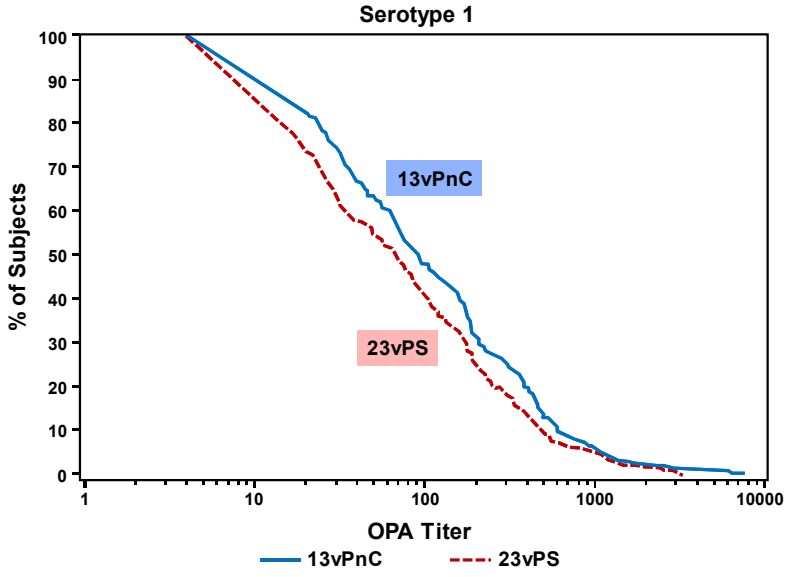


Figure 4-8: Study 3005 – Preimmunized Subjects ≥70 yo, OPA RCDCs 1 Month After 13vPnC or 23vPS, Serotypes 3, 4, 5, 6A

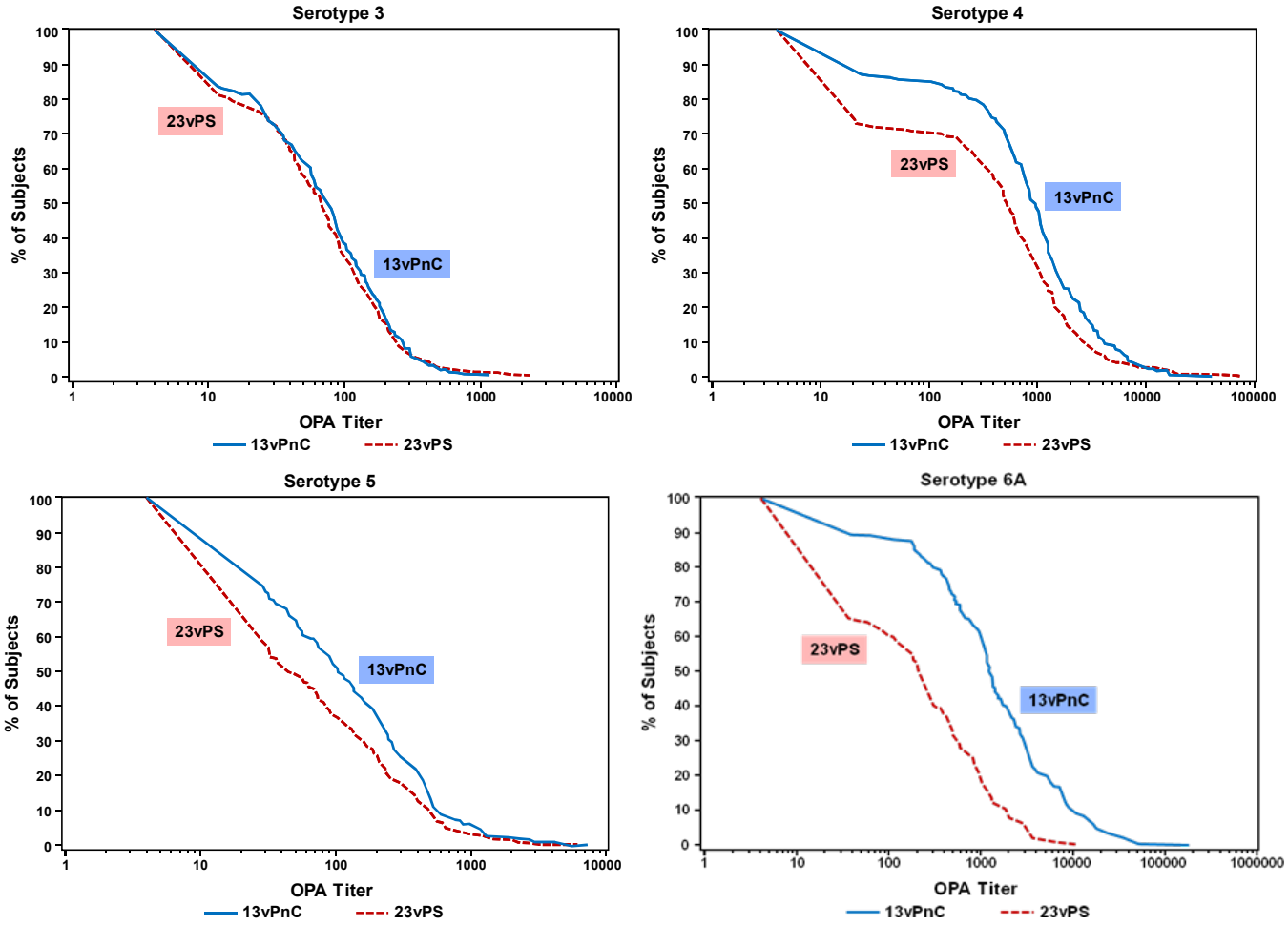


Figure 4-9: Study 3005 – Preimmunized Subjects ≥70 yo, OPA RCDCs 1 Month After 13vPnC or 23vPS, 6B, 7F, 9V, 14

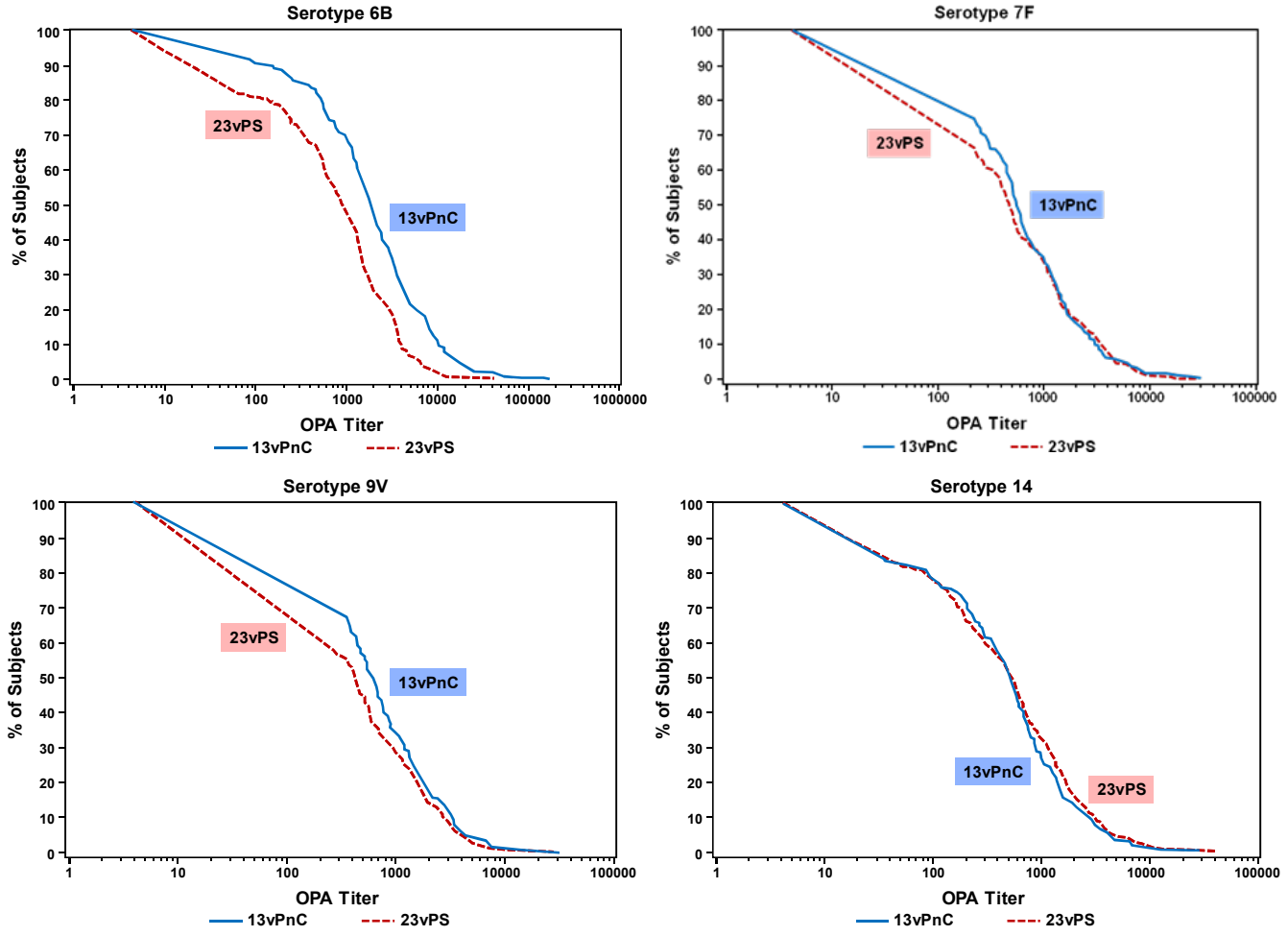
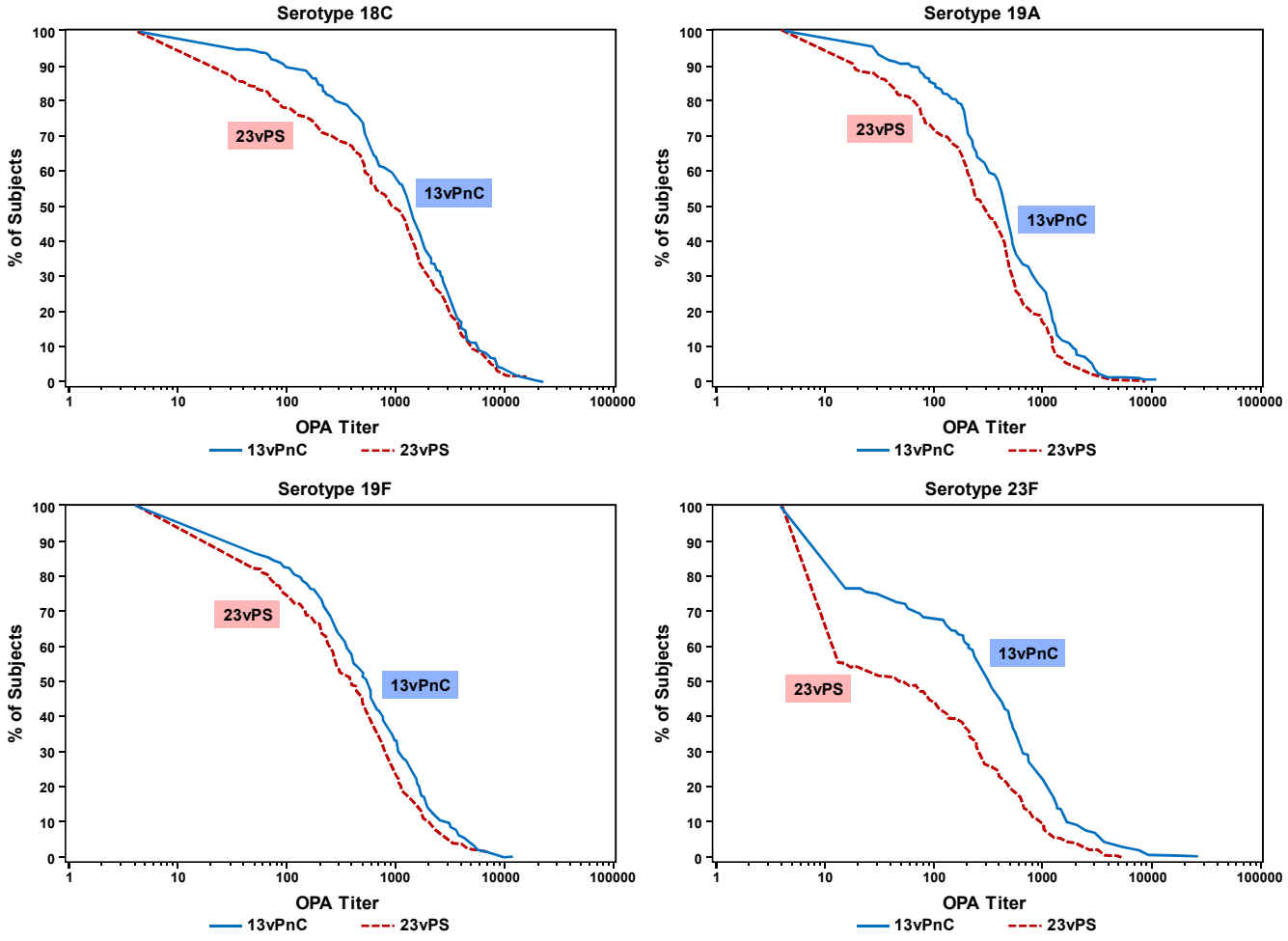


Figure 4-10: Study 3005 – Preimmunized Subjects ≥70 yo, OPA RCDCs 1 Month After 13vPnC or 23vPS, 18C, 19A, 19F, 23F



4.3.2.4 Immunogenicity Conclusions After a Single Study Dose of 13vPnC in Pneumococcal Vaccine-Experienced Adults ≥ 70 Years of Age, Study 3005, Year 0, Study 3005

All primary and secondary objectives were achieved in study 3005 for a single study dose of 13vPnC. In adults ≥70 years of age immunized at least 5 years earlier with 23vPS vaccine, single study dose 13vPnC immune response was non-inferior to single dose 23vPS response for the 12 common serotypes as measured by geometric mean ratio (GMR), and 13vPnC was statistically significantly more immunogenic than 23vPS for most of the 12 common serotypes when measured by GMRs or proportion of responders. For most comparisons in preimmunized elderly after a single dose of 13vPnC or 23vPS, OPA titers were higher throughout the full range of OPA responses; 13vPnC is likely to afford better protection than 23vPS against the 12 common serotypes, in adults previously immunized with 23vPS vaccine. OPA response to serotype 6A after 13vPnC was consistently greater than that after 23vPS and all serotype 6A study objectives were achieved.

4.3.3 Overall Conclusions Regarding Evidence to Support a Single Dose of 13vPnC for Vaccination of Pneumococcal Vaccine-Naïve Adults or Revaccination of 23vPS-Experienced Adults, Studies 004 and 3005

Both the 004 and 3005 trials achieved all primary and secondary objectives. 13vPnC was consistently observed to induce a non-inferior OPA response in pneumococcal vaccine-naïve subjects and a non-inferior OPA response in 23vPS-experienced subjects in comparison to 23vPS vaccine, as demonstrated by comparison of OPA geometric mean titers (GMTs) and proportion of OPA assay responders. Moreover, in every instance, superiority of response elicited by 13vPnC was demonstrated for most serotypes. For both pneumococcal vaccine-naïve older adults and 23vPS-experienced adults, comparative OPA responses indicate that a dose of 13vPnC is likely to provide protection against IPD that is at least as good as and most likely better than that provided by 23vPS for the serotypes in common.

4.4 Evidence That 13vPnC/13vPnC is Preferred to 23vPS/13vPnC for Reimmunization of Adults ≥70 Years of Age Who Received 23vPS at Least 5 Years Earlier, to Maintain Optimum Antibody Response Against Serotypes in Common, Study 3005

All primary and secondary objectives were achieved in both years for study 3005.

The design of the 3005 study is shown in Figure 4-11 below. Results after a dose of 13vPnC in year 1 in groups 1 and 2, will be discussed in this section.

Figure 4-11: Study 3005 Design

Study Design				
Subjects	**Group**	**N**	**Year 0**	**Year 1**
Prior PS ≥5 Years	**1**	**462**	**13vPnC**	**13vPnC**
	2	**462**	**23vPS**	**13vPnC**

4.4.1 Key Immunogenicity Objectives and Results After a Study Dose of 13vPnC Administered 1 Year After Either 13vPnC or 23vPS, Study 3005

The immune response to a second dose of 13vPnC administered 1 year after an initial study dose of 13vPnC is non-inferior to the immune response to the initial study dose of 13vPnC as measured by serotype-specific OPA titers obtained 1 month after vaccination (secondary objective) (Table 4-7**).** This objective was met for all serotypes. Although not a predefined objective, OPA responses to a second dose of 13vPnC were statistically significantly greater than the immune responses to an initial 13vPnC dose for serotypes 6A, 6B and 23F; the lower limit of the 2-sided, 95% CI for the GMR was >1 for each of these serotypes (1.03, 1.02, and 1.60, respectively). OPA responses to 13vPnC/13vPnC were marginally lower compared to those after 13vPnC for serotypes 4 and 5 (upper limit of 95% CI <1; 0.92 and 0.94, respectively). The statistically greater immune response after 13vPnC compared to 23vPS observed after the first dose was maintained after a second dose of 13vPnC one year later. Hence, in this population of 23vPS-preimmunized adults ≥70 years of age, administration of 13vPnC establishes an immunological state that results in comparable responses to a second dose of 13vPnC delivered 1 year after the first dose.

Table 4-7: Study 3005 – Preimmunized Subjects ≥70 yo, OPA GMTs 13vPnC/13vPnC vs 13vPnC

Serotype	13vPnC/13vPnC GMT	13vPnC GMT	GMT Ratio	(95% CI)
1	76	79	1.0	(0.85, 1.10)
3	55	55	1.0	(0.91, 1.11)
4	487	614	0.8	(0.68, 0.92)
5	57	69	0.8	(0.73, 0.94)
6A	1169	971	1.2	(1.03, 1.40)
6B	1590	1358	1.2	(1.02, 1.35)
7F	180	222	0.8	(0.65, 1.01)
9V	166	187	0.9	(0.69, 1.15)
14	241	265	0.9	(0.79, 1.05)
18C	1003	918	1.1	(0.97, 1.23)
19A	341	349	1.0	(0.89, 1.07)
19F	322	329	1.0	(0.83, 1.15)
23F	309	167	1.9	(1.60, 2.14)

- **Non-inferiority criteria met for all serotypes**

Note: For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.

The immune response to a dose of 13vPnC administered 1 year after the study dose of 23vPS relative to the immune response to an initial study dose of 13vPnC was evaluated, as measured by serotype-specific OPA titers obtained 1 month after vaccination (exploratory objective). In contrast to the comparable OPA response after the 13vPnC/13vPnC sequence compared to the first dose of 13vPnC, OPA responses to a dose of 13vPnC given after 23vPS were statistically significantly lower than the immune response to an initial 13vPnC dose for all 13 serotypes; the upper limit of the 2-sided, 95% CI for the GMR (23vPS/13vPnC GMT/13vPnC GMT) was <1 for each serotype (Table 4-8). These observations support the perspective that in adults ≥70 years of age preimmunized with 23vPS vaccine at least 5 years earlier, an additional 23vPS vaccine dose diminishes response to subsequent 13vPnC administered 1 year later compared to an initial study dose of 13vPnC. This provides additional support for administration

of 13vPnC to 23vPS-experienced adults whenever possible in preference to a second dose of 23vPS.

Table 4-8: Study 3005 – Preimmunized Subjects ≥70 yo, OPA GMTs 23vPS/13vPnC vs 13vPnC

Serotype	23vPS/13vPnC GMT	13vPnC GMT	GMT Ratio	(95% CI)
1	34	81	0.4	(0.33 , 0.54)
3	33	55	0.6	(0.49 , 0.74)
4	267	545	0.5	(0.36 , 0.67)
5	42	72	0.6	(0.44 , 0.76)
6B	721	1261	0.6	(0.42 , 0.78)
7F	120	245	0.5	(0.34 , 0.71)
9V	72	181	0.4	(0.27 , 0.59)
14	194	280	0.7	(0.51 , 0.95)
18C	513	907	0.6	(0.43 , 0.74)
19A	248	354	0.7	(0.56 , 0.86)
19F	180	333	0.5	(0.40 , 0.72)
23F	87	158	0.6	(0.39 , 0.78)
6A	549	903	0.6	(0.44 , 0.83)

- Responses to all 13 serotypes statistically significantly lower for 23v/13v compared to 13v

The immune response to a second dose of 13vPnC administered 1 year after the initial study dose of 13vPnC is statistically significantly greater than the immune response to a study dose of 13vPnC administered 1 year after the initial study dose of 23vPS for 11 of 12 serotypes, as measured by serotype-specific OPA titers obtained 1 month after vaccination (exploratory objective) (Table 4-9**).** These results further illustrate an important distinction between the vaccination sequence of 13vPnC/13vPnC compared to 23vPS/13vPnC: a prior dose of 13vPnC is not associated with a reduced immune response following a second dose of 13vPnC, in contrast to the effect seen in subjects who received a study dose of 23vPS and then experienced reduced responses upon follow-on administration of 13vPnC. These findings

support the perspective that 13vPnC followed by 13vPnC revaccination maintains antibody response in 23vPS-preimmunized adults, well above antibody responses possible after 23vPS/13vPnC, and is the preferred approach to optimize protection.

Table 4-9: Study 3005 – Preimmunized Subjects ≥70 yo, OPA GMTs 13vPnC/13vPnC vs 23vPS/13vPnC

Serotype	13vPnC/13vPnC GMT	23vPS/13vPnC GMT	GMT Ratio	(95% CI)
1	76	34	2.2	(1.74, 2.82)
3	55	33	1.7	(1.36, 2.03)
4	472	267	1.8	(1.29, 2.42)
5	56	42	1.4	(1.03, 1.79)
6B	1565	721	2.2	(1.61, 2.94)
7F	185	120	1.5	(1.05, 2.24)
9V	158	72	2.2	(1.47, 3.32)
14	238	194	1.2	(0.89, 1.68)
18C	975	513	1.9	(1.45, 2.49)
19A	339	248	1.4	(1.11, 1.68)
19F	311	180	1.7	(1.30, 2.30)
23F	310	87	3.6	(2.57, 4.93)
6A	1134	549	2.1	(1.54, 2.77)

- 12 of 13 serotypes statistically significantly greater for 13vPnC/13vPnC vs 23vPS/13vPnC

4.4.2 Summary of Additional Immunogenicity Objectives and Results After a Study Dose of 13vPnC Administered 1 Year After Either 13vPnC or 23vPS, Study 3005

The immune response to a second dose of 13vPnC administered 1 year after an initial study dose of 13vPnC is non-inferior to the immune response to 23vPS (year 0) for the 12 common serotypes contained in 13vPnC as measured by serotype-specific OPA titers obtained 1 month after vaccination (secondary objective). OPA response after the second dose of 13vPnC vaccine was non-inferior to the response after the first study dose of 23vPS for the 12 serotypes in common when administered to 23vPS-preimmunized adults ≥70 years of age. Although not a predefined objective, OPA response to a second dose of 13vPnC was statistically

significantly greater than the immune response to an initial study dose of 23vPS for 9 of 12 common serotypes, excluding serotypes 3, 7F, and 14. These findings are consistent with maintenance of statistically greater OPA responses for most common serotypes after 2 successive doses of 13vPnC spaced 1 year apart compared to those of 23vPS vaccine recipients.

The anti-6A titer in recipients of a second dose of 13vPnC administered 1 year after the initial study dose of 13vPnC is statistically significantly greater than the anti-6A titer in recipients of an initial study dose of 23vPS (year 0), measured 1 month after vaccination (secondary objective). The second 13vPnC study dose was statistically significantly more immunogenic than the year 0, 23vPS dose for serotype 6A, as measured by GMR.

Antibody responses were assessed 1 year after initial study vaccination as measured by serotype-specific OPA titers obtained before year 1 study vaccination (exploratory objective). OPA GMTs declined over the year from 1 month after vaccination 1 to the day of vaccination 2 one year later. At that time, point estimates for OPA GMTs were higher in the 13vPnC group compared to the 23vPS group for 11 of 12 serotypes in common (exception serotype 14) and for 3 of these 11 serotypes (4, 6B, 23F) the 95% CIs for the 2 vaccine groups did not overlap. As expected, OPA GMTs elicited by serotype 6A were substantially higher at each time point in the subjects receiving 13vPnC than in those receiving 23vPS.

Figure 4-12 to Figure 4-15 permit comparisons of OPA antibody titers before and after each vaccination.

Figure 4-12: Study 3005 – Preimmunized Subjects ≥70 yo, OPA Antibody Response Curves, Serotypes 1, 3, 4, 5

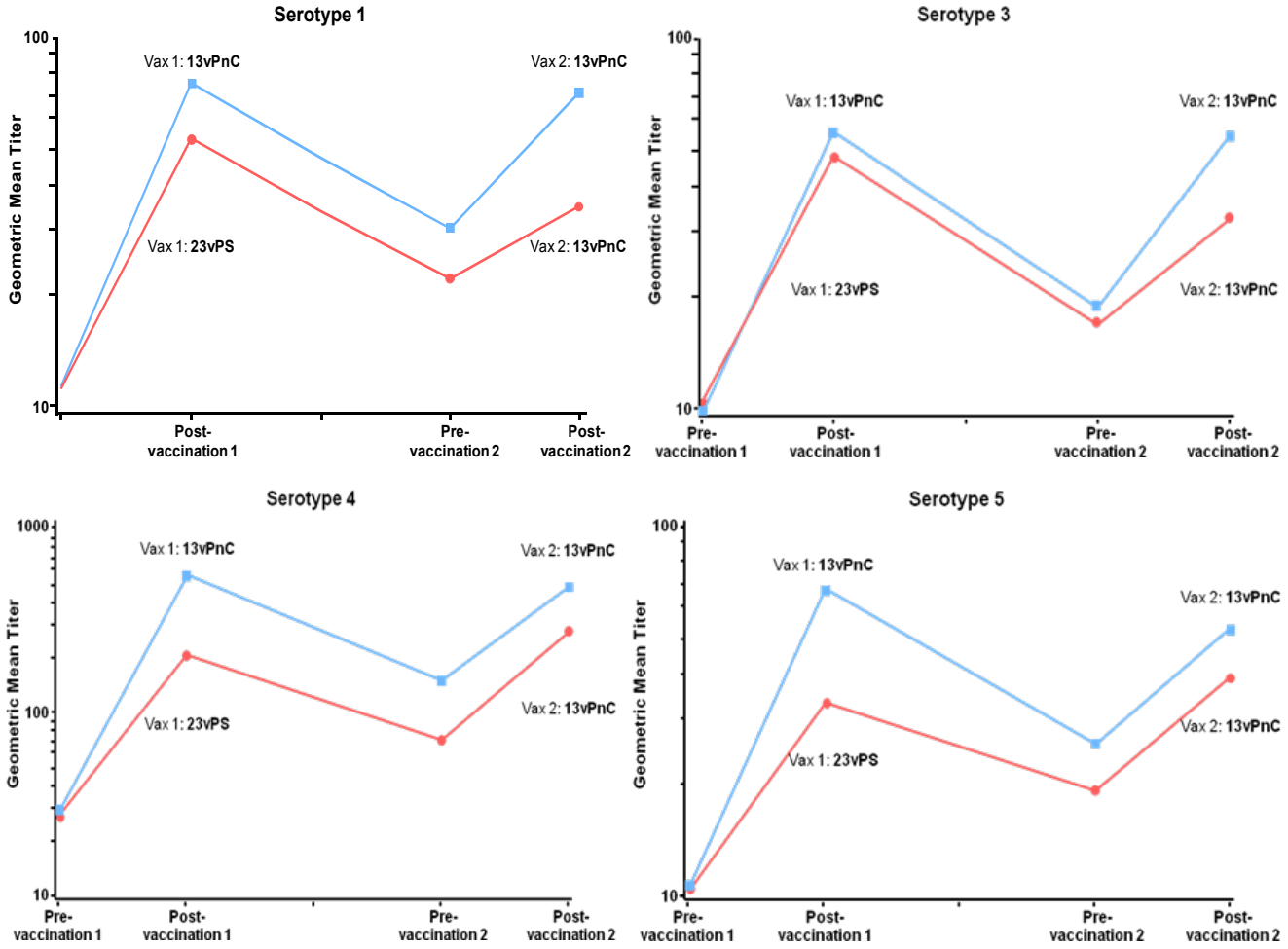


Figure 4-13: Study 3005 – Preimmunized Subjects ≥70 yo, OPA Antibody Response Curves, Serotypes 6A, 6B, 7F, 9V

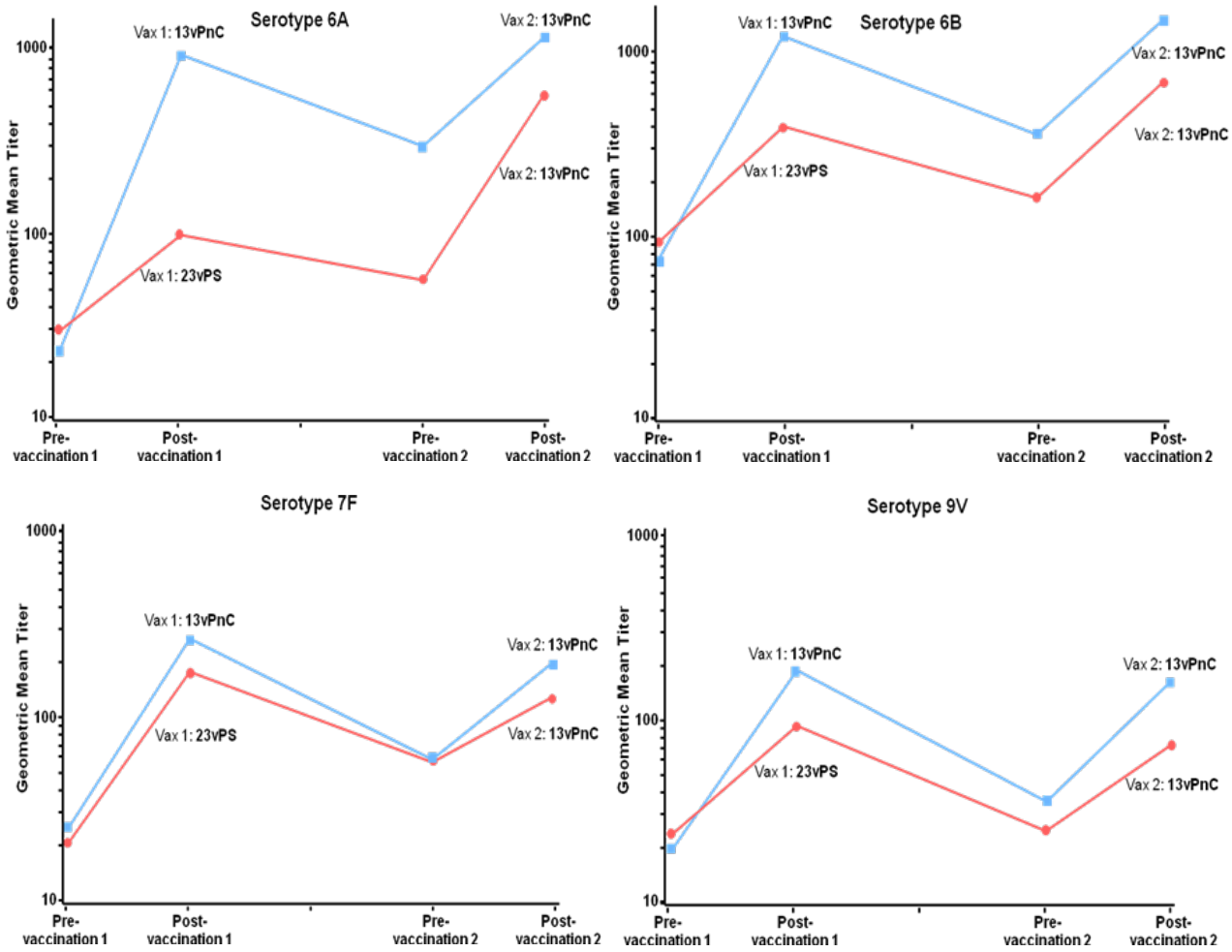


Figure 4-14: Study 3005 – Preimmunized Subjects ≥70 yo, OPA Antibody Response Curves, Serotypes 14, 18C, 19A, 19F

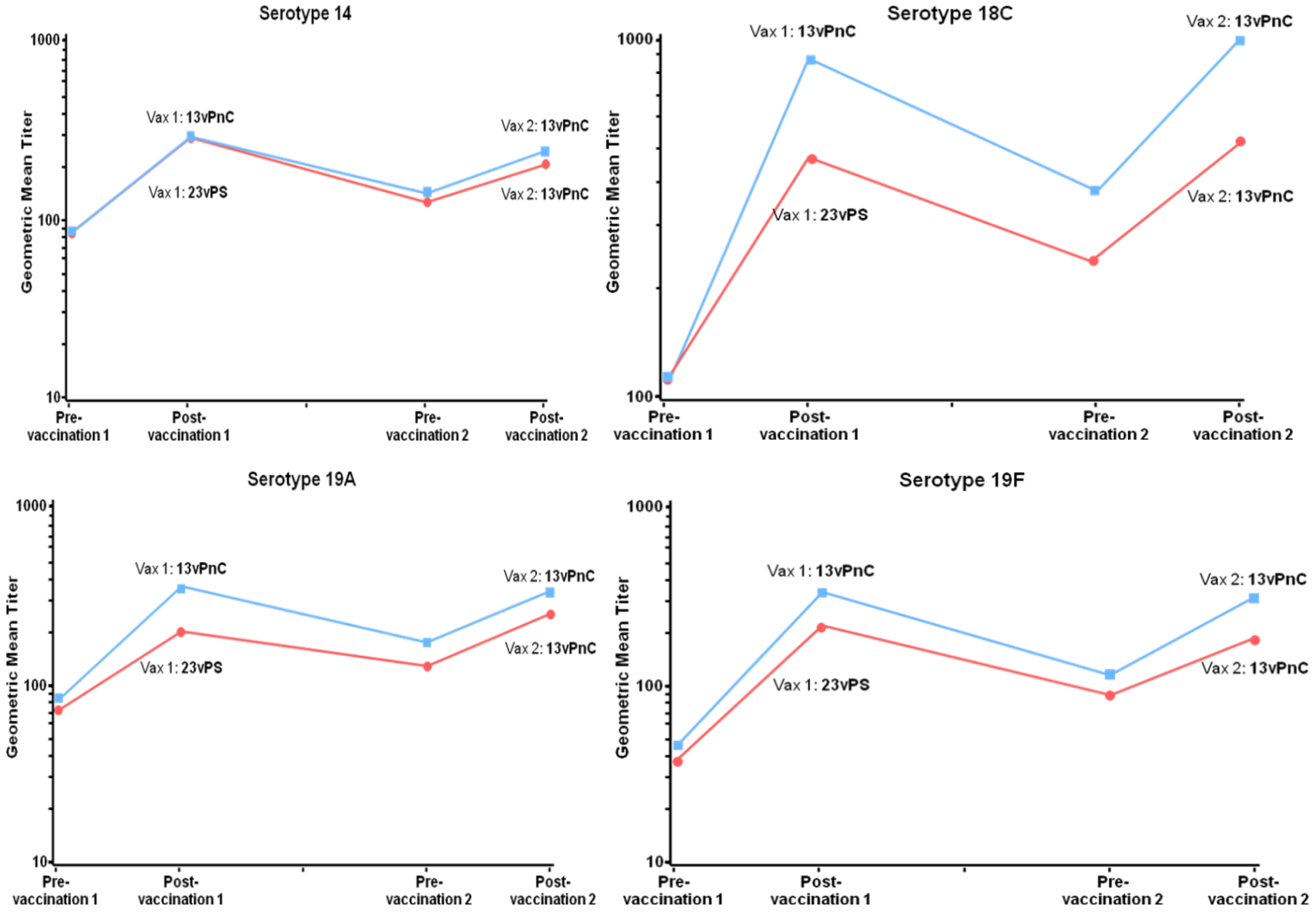
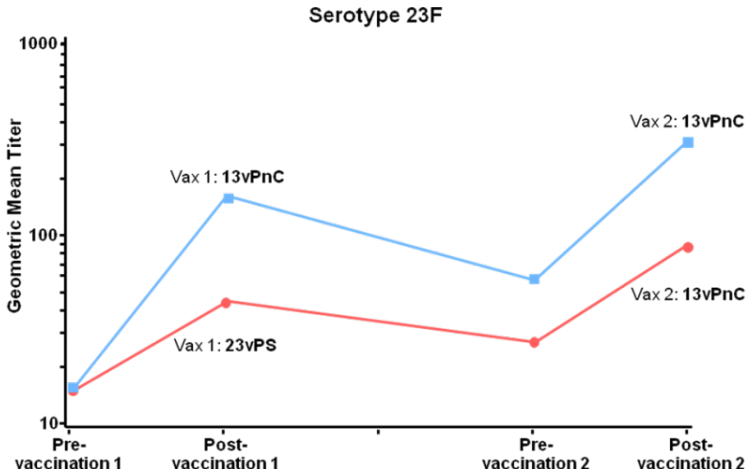


Figure 4-15: Study 3005 – Preimmunized Subjects ≥70 yo, OPA Antibody Response Curves, Serotype 23F



4.4.3 Overall Immunogenicity Conclusions After a Study Dose of 13vPnC Administered 1 Year After Either a Study Dose of 13vPnC or 23vPS in 23vPS-Preimmunized Subjects, Study 3005

The immune response to a second dose of 13vPnC administered 1 year after an initial study dose of 13vPnC in comparison to the OPA response to the initial study dose of 13vPnC met the prespecified non-inferiority criteria for all 13 serotypes in preimmunized subjects. The immune response to a second dose of 13vPnC administered 1 year after an initial study dose of 13vPnC is non-inferior to the immune response to 23vPS (year 0) and is statistically greater for 9 of 12 common serotypes. In contrast, OPA responses to a dose of 13vPnC one year after 23vPS were statistically significantly lower than the immune response to an initial 13vPnC dose for 11 of 12 common serotypes, excluding serotype 14. Antibody levels decreased over time for both vaccine groups after vaccination 1, but remained higher for the 13vPnC/13vPnC group compared to the 23vPS group at all time points for most serotypes. A prior dose of 13vPnC does not appear to negatively influence the immune responses to a second dose of 13vPnC, whereas a prior dose of 23vPS results in lower responses to a subsequent dose of 13vPnC. These findings indicate that 13vPnC is better suited than 23vPS to re-establish immune response, to common serotypes in 23vPS-preimmunized older adults, and that these improved responses can be maintained with

subsequent 13vPnC, affording the potential to extend protection not achievable with 23vPS revaccination.

4.5 Evidence that 13vPnC Establishes Memory and Permits Revaccination to Maintain Optimum Immune Response Not Possible with 23vPS in Pneumococcal Vaccine-Naïve Adults, Studies 3010, 004 Extension

4.5.1 Key Immunogenicity Objectives and Results After 13PnC/23vPS or 23vPS/13vPnC With a 1-Year Interval Between Doses, Study 3010

The 3010 study evaluated the safety, tolerability, and immunogenicity data of 13vPnC when administered as a 2-dose regimen, with doses spaced 1 year apart. Immunization sequences of 13vPnC/13vPnC, 13vPnC/23vPS, and 23vPS/13vPnC were evaluated in adults aged 60 years to 64 years who were naïve to pneumococcal vaccine. The 1-year interval was chosen to provide an assessment of the potential impact of the initial vaccine on subsequent vaccine response in this population, based on prior experience with 7vPnC. The design of 3010 is shown in Figure 4-16.

Figure 4-16: Study 3010 Design

Study Design			
Group	**N**	**Year 0**	**Year 1**
1	**480**	**13vPnC**	**13vPnC**
			23vPS
2	**240**	**23vPS**	**13vPnC**

Study 3010 met both primary objectives and their associated secondary objectives.

The immune response to 23vPS administered 1 year after an initial study dose of 13vPnC is as immunogenic as the immune response to an initial study dose of 23vPS for the 12 common serotypes as measured by serotype-specific OPA titers obtained 1 month after vaccination. That is, the lower bound of the 95% CI of the geometric mean ratio of the GMTs ($GMT_{13vPnC/23vPS}/GMT_{23vPS}$) is greater than 0.5 (2-fold criterion) (1st of 2 coprimary objectives). This non-inferiority criterion was achieved for all 12 common serotypes (Table 4-10)

23vPS administered 1 year after an initial study dose of 13vPnC is statistically significantly more immunogenic than an initial study dose of 23vPS for at least some of the 12 common serotypes as measured by serotype-specific OPA titers obtained 1 month after vaccination ($GMT_{13vPnC/23vPS}/GMT_{23vPS}$) (secondary objective) (Table 4-10, shaded). OPA responses were statistically significantly greater after 13vPnC/23vPS relative to 23vPS for 6 of 12 serotypes. These findings indicate that 13vPnC augments immune response to a subsequent dose of 23vPS administered 1 year later for serotypes in common compared to 23vPS alone, consistent with establishment of a memory response to polysaccharides in common.

Table 4-10: Study 3010 – Naïve Subjects 60-64 yo, OPA GMTs, 13vPnC/23vPS vs 23vPS

Serotype	13vPnC/23vPS GMT	23vPS GMT	GMT Ratio	(95% CI)
1	148	148	1.0	(0.75, 1.33)
3	125	80	1.6	(1.24, 1.94)
4	1385	1357	1.0	(0.74, 1.41)
5	199	140	1.4	(1.01, 2.00)
6B	1215	706	1.7	(1.18, 2.51)
7F	537	331	1.6	(1.07, 2.47)
9V	373	288	1.3	(0.79, 2.12)
14	622	734	0.8	(0.58, 1.25)
18C	1062	789	1.3	(0.94, 1.93)
19A	467	376	1.2	(0.96, 1.61)
19F	774	509	1.5	(1.09, 2.12)
23F	198	70	2.8	(1.86, 4.35)

- Non-inferiority criterion met for all 12 common serotypes
- Response to 6 of 12 serotypes statistically significantly greater for 13vPnC/23vPS vs 23vPS

The immune response to 23vPS administered 1 year after an initial study dose of 13vPnC is non-inferior to the immune response to an initial study dose of 13vPnC for most but not all of the 12 common serotypes as measured by serotype-specific OPA titers 1 month after vaccination. That is, the lower bound of the 95% CI of the GMFR ($GMT_{13vPnC/23vPS}/GMT_{13vPnC}$) is greater than 0.5 (secondary objective).

The non-inferiority criterion was met for serotypes 1, 3, 5, 6B, 14, 18C, 19A, and 19F, but was missed by a small margin for serotypes 4, 7F, 9V, and 23F, for which the lower limits of the 95% CIs were 0.49, 0.35, 0.41, and 0.50, respectively (Table 4-11). Although the improved responses after 13vPnC/23vPS compared to 23vPS alone described above establish evidence of memory after 13vPnC, it is hypothesized that high antibody titers after 13vPnC at the time of immunization may have limited full potential response to 23vPS when administered over the short interval of 1 year. Since circulating antibody declines over time, lengthening the interval between doses is likely to optimize response to a follow-on 23vPS immunization. We have demonstrated this in an extension of the 004 study described below (4.5.5). It is quite clear that the response to 13vPnC/23vPS is generally statistically greater than response after 23vPS/13vPnC, as noted by fulfillment of the following objectives.

Table 4-11: Study 3010 – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC vs 13vPnC/23vPS

Serotype	13vPnC/23vPS GMT	13vPnC GMT	GMT Ratio	(95% CI)
1	140	220	0.6	(0.55, 0.75)
3	129	74	1.7	(1.52, 2.01)
4	1430	2517	0.6	(0.49, 0.66)
5	188	227	0.8	(0.67, 1.03)
6B	1351	2012	0.7	(0.57, 0.79)
7F	533	1252	0.4	(0.35, 0.52)
9V	406	758	0.5	(0.41, 0.69)
14	616	664	0.9	(0.75, 1.15)
18C	1074	1532	0.7	(0.58, 0.85)
19A	457	696	0.7	(0.58, 0.74)
19F	773	696	1.1	(0.89, 1.39)
23F	216	358	0.6	(0.50, 0.73)

- Non-inferiority met for 8 of 12 common serotypes
- 4 of 12 common serotypes did not meet the non-inferiority criterion

Note: For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.

The immune response to 23vPS administered 1 year after an initial study dose of 13vPnC is non-inferior to the immune response to 13vPnC administered 1 year after an initial study dose of 23vPS for the 12 common serotypes in 13vPnC, as measured by serotype-specific OPA titers 1 month after vaccination. That is, the lower bound of the 95% CI of the geometric mean ratio ($GMT_{13vPnC/23vPS}/GMT_{23vPS/13vPnC}$) is greater than 0.5 (2-fold criterion) (2st of 2 coprimary objectives). This non-inferiority objective was achieved for all 12 common serotypes (Table 4-12).

23vPS administered 1 year after an initial study dose of 13vPnC is statistically significantly more immunogenic than 13vPnC administered 1 year after an initial study dose of 23vPS for at least some of the 12 common serotypes as measured by serotype-specific OPA titers obtained 1 month after vaccination ($GMT_{13vPnC/23vPS}/GMT_{23vPS/13vPnC}$) (secondary objective) (Table 4-12, shaded). After vaccination 2, 13vPnC/23vPS elicited statistically significantly greater responses than 23vPS/13vPnC for 11 of the 12 common serotypes.

Table 4-12: Study 3010 – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC/23vPS vs 23vPS/13vPnC

Serotype	13vPnC/23vPS GMT	23vPS/13vPnC GMT	GMT Ratio	(95% CI)
1	148	77	1.9	(1.43, 2.57)
3	125	50	2.5	(1.95, 3.16)
4	1385	935	1.5	(1.12, 1.96)
5	199	85	2.4	(1.67, 3.31)
6B	1215	710	1.7	(1.19, 2.47)
7F	537	126	4.3	(2.76, 6.61)
9V	373	114	3.3	(1.97, 5.45)
14	622	435	1.4	(0.98, 2.10)
18C	1062	564	1.9	(1.32, 2.69)
19A	467	289	1.6	(1.27, 2.07)
19F	774	286	2.7	(1.96, 3.74)
23F	198	124	1.6	(1.05, 2.45)

- Non-inferiority criterion met for all 12 common serotypes
- Response to 11 of 12 serotypes statistically significantly greater for 13vPnC/23vPS vs 23vPS/13vPnC

An initial dose of 13vPnC is statistically significantly more immunogenic than 13vPnC administered 1 year after an initial dose of 23vPS for at least some of the 12 common serotypes as measured by serotype-specific OPA titers 1 month after vaccination ($GMT_{13vPnC}/GMT_{23vPS/13vPnC}$) (secondary objective). The lower limits of the 95% CIs for the ratios were greater than 1.0 for all 12 common serotypes, indicating that 13vPnC responses were statistically significantly greater than 23vPS/13vPnC responses (Table 4-13).

Table 4-13: Study 3010 – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC vs 23vPS/13vPnC

Serotype	13vPnC GMT	23vPS/13vPnC GMT	Ratio	(95% CI)
1	207	77	2.7	(2.03, 3.55)
3	75	50	1.5	(1.18, 1.89)
4	2536	935	2.7	(2.07, 3.55)
5	215	85	2.5	(1.77, 3.61)
6B	1948	710	2.7	(1.94, 3.88)
7F	1063	126	8.5	(5.68, 12.60)
9V	767	114	6.7	(4.45, 10.22)
14	650	435	1.5	(1.02, 2.18)
18C	1576	564	2.8	(2.01, 3.89)
19A	709	289	2.5	(1.92, 3.13)
19F	711	286	2.5	(1.80, 3.44)
23F	354	124	2.9	(1.92, 4.28)

- Responses to all 12 common serotypes statistically significantly higher for 13vPnC compared to 23vPS/13vPnC

4.5.2 Conclusions from Evaluation of Sequential Dosing of 13vPnC and 23vPS With a 1-Year Interval Between Doses, Study 3010

In pneumococcal vaccine-naïve adults, 13vPnC establishes memory and augments response to subsequent 23vPS for polysaccharides in common compared to 23vPS alone. In contrast,

13vPnC/23vPS administered over an interval of 1 year did not uniformly induce a comparable or higher antibody response compared to the first dose of 13vPnC. As noted in experiments from others, cited in Section 2.4.2, conjugate pneumococcal vaccine followed by 23vPS by an interval of less than 1 year, did not appear to boost 23vPS responses.

Therefore, it was hypothesized that responses to 23vPS in the sequence 13vPnC/23vPS might be further improved if the interval between doses was lengthened, inducing responses after 23vPS comparable or greater than after the first dose of 13vPnC.

This hypothesis was confirmed by an extension of study 004 (Section 4.5.5). It is clear that the overall establishment of memory and positive influence of prior 13vPnC on subsequent 23vPS is dramatically different than the negative influence of the 23vPS/13vPnC sequence. 23vPS is unable to establish immunologic memory in pneumococcal vaccine-naïve adults and the negative immunologic consequence of 23vPS/13vPnC administration on subsequent immune response is similar to that observed in study 3005. Hence, 13vPnC alone or the sequence 13vPnC/23vPS is much preferred to the sequence of 23vPS/13vPnC for induction of immunologic memory and optimum functional antibody response to serotypes in common.

4.5.3 Key Immunogenicity Objectives and Results after 13PnC/13vPnC or 23vPS/13vPnC With a 1-Year Interval Between Doses, Study 3010

In adults ≥70 years of age who received 23vPS at least 5 years earlier, 13vPnC/13vPnC, with doses spaced 1 year apart (see study 3005 results, Section 4.4), induced antibody responses after a second dose that were comparable to those after a first dose, and 13vPnC/13vPnC elicited responses that were clearly superior to responses after 23vPS/13vPnC. These findings indicate that 13vPnC is better suited than 23vPS to re-establish, maintain, and potentially improve response to common serotypes in 23vPS-preimmunized older adults. It is also reasonable to evaluate the sequence of 13vPnC/13vPnC (doses spaced 1 year apart) compared to the first dose of 13vPnC and compared to 23vPS/13vPnC (doses spaced 1 year apart) in pneumococcal vaccine-naïve adults. These investigations were included in objectives for study 3010. The study design is illustrated in Figure 4-17.

Figure 4-17: Study 3010 Design

Study Design			
Group	**N**	**Year 0**	**Year 1**
1	**480**	**13vPnC**	**13vPnC**
			23vPS
2	**240**	**23vPS**	**13vPnC**

The immune response to a second dose of 13vPnC administered 1 year after an initial study dose of 13vPnC is non-inferior to the immune response to the initial dose of 13vPnC for *most but not all* serotypes, as measured by serotype-specific OPA titers 1 month after the year 0 and year 1 vaccinations. That is, the lower bound of the 95% CI of the geometric mean fold rise (GMFR; $GMT_{13vPnC/13vPnC}/GMT_{13vPnC}$) is greater than 0.5 (secondary objective). Prespecified noninferiority criteria were achieved for 8 of 12 serotypes, but missed for 4, 5, 7F and 9V (Table 4-14).

Table 4-14: Study 3010 – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC/13vPnC vs 13vPnC

Serotype	13vPnC/13vPnC GMT	13vPnC GMT	GMT Ratio	(95% CI)
1	142	215	0.7	(0.54, 0.82)
3	89	73	1.2	(0.99, 1.49)
4	1214	2255	0.5	(0.43, 0.68)
5	98	170	0.6	(0.43, 0.77)
6A	2281	2682	0.9	(0.67, 1.08)
6B	1882	2112	0.9	(0.71, 1.12)
7F	323	930	0.3	(0.24, 0.49)
9V	335	919	0.4	(0.26, 0.51)
14	384	492	0.8	(0.60, 1.02)
18C	986	1440	0.7	(0.54, 0.87)
19A	385	583	0.7	(0.53, 0.82)
19F	502	566	0.9	(0.69, 1.15)
23F	456	291	1.6	(1.15, 2.13)

- **OPA GMTs were lower for 11 of 13 serotypes for 13vPnC/13vPnC compared to 13vPnC**
- **Serotypes 4, 5, 7F and 9V were below the lower limit of 2-sided 95% CI of 0.5**

Note: For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.

Comparison of the sequences of 13vPnC/13vPnC and 23vPS/13vPnC in the 3010 trial revealed that prior 23vPS had a significantly greater negative impact on subsequent administration of 13vPnC one year later. Comparison of OPA responses between the 13vPnC/13vPnC and the 23vPS/13vPnC groups (Table 4-15) revealed that the responses in the former group were statistically significantly greater for 10 of the 13 serotypes.

Table 4-15: Study 3010 – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC/13vPnC vs 23vPS/13vPnC

Serotype	13vPnC/13vPnC GMT	23vPS/13vPnC GMT	GMT Ratio	(95% CI)
1	139	77	1.8	(1.27, 2.56)
3	89	50	1.8	(1.33, 2.36)
4	1212	935	1.3	(0.91, 1.85)
5	96	85	1.1	(0.73, 1.76)
6A	2354	1133	2.1	(1.43, 3.03)
6B	1879	710	2.6	(1.74, 4.03)
7F	335	126	2.7	(1.51, 4.70)
9V	356	114	3.1	(1.72, 5.69)
14	389	435	0.9	(0.56, 1.43)
18C	1015	564	1.8	(1.16, 2.78)
19A	410	289	1.4	(1.05, 1.91)
19F	501	286	1.8	(1.18, 2.61)
23F	472	124	3.8	(2.33, 6.25)

- Non-inferiority criterion met for all 13 serotypes
- Response to 10 of 13 serotypes statistically significantly greater for 13vPnC/13vPnC vs 23vPS/13vPnC

4.5.4 Conclusions from Evaluation of Sequential Dosing of 13vPnC/13vPnC Compared to 23vPS/13vPnC With a 1-Year Interval Between Doses, Study 3010

13vPnC/13vPnC is associated with a somewhat diminished antibody response for a number of serotypes when a second dose is given a year later. However, a fundamental difference exists for the impact of 23vPS on subsequent administration of 13vPnC compared to 13vPnC on subsequent 13vPnC. Findings support the perspective that 13vPnC/13vPnC is preferred to 23vPS/13vPnC for establishment and maintenance of immune response. The negative effect of 23vPS is likely related to the inability of this vaccine to establish memory and is supported by the negative effect on immune response seen for both 23vPS/13vPnC in this trial and historical 23vPS/23vPS studies, due to the T-cell-independent nature of response. In contrast, the ability of 13vPnC to boost 23vPS response and elicit memory is apparent from the 3010 data, so an alternative potential mechanism for blunting of response to a second dose of 13vPnC after 1 year

was proposed. The robust nature of the immune response and higher antibody titers achieved after the first 13vPnC dose in naïve adults may interfere with subsequent 13vPnC vaccination, particularly given the narrow 1-year interval between doses. This hypothesis gains support from observations in the 3005 trial, in which lower responses were seen in these older 23vPS-preimmunized subjects after the first 13vPnC dose compared to naïve adults, presumed due to a combination of the blunting effect of the prior 23vPS and older age. In this circumstance, responses after a second study dose of 13vPnC recovered to prior levels.

This suggests that after a first 13vPnC dose a longer interval between doses, and consequent lower antibody titers at the time of the subsequent 13vPnC (or 23vPS) dose, might be associated with improvement in the second vaccine response, and optimize antibody response to extend protection.

Figure 4-18 to Figure 4-21 provide descriptive comparisons of antibody responses before and after each vaccination for each of the experimental groups. These plots also display comparisons of 6A responses, which fulfilled exploratory objectives demonstrating the benefit of 13vPnC.

Figure 4-18: Study 3010 – Naïve Subjects 60-64 yo, OPA Antibody Response Curves, Serotypes 1, 3, 4, 5

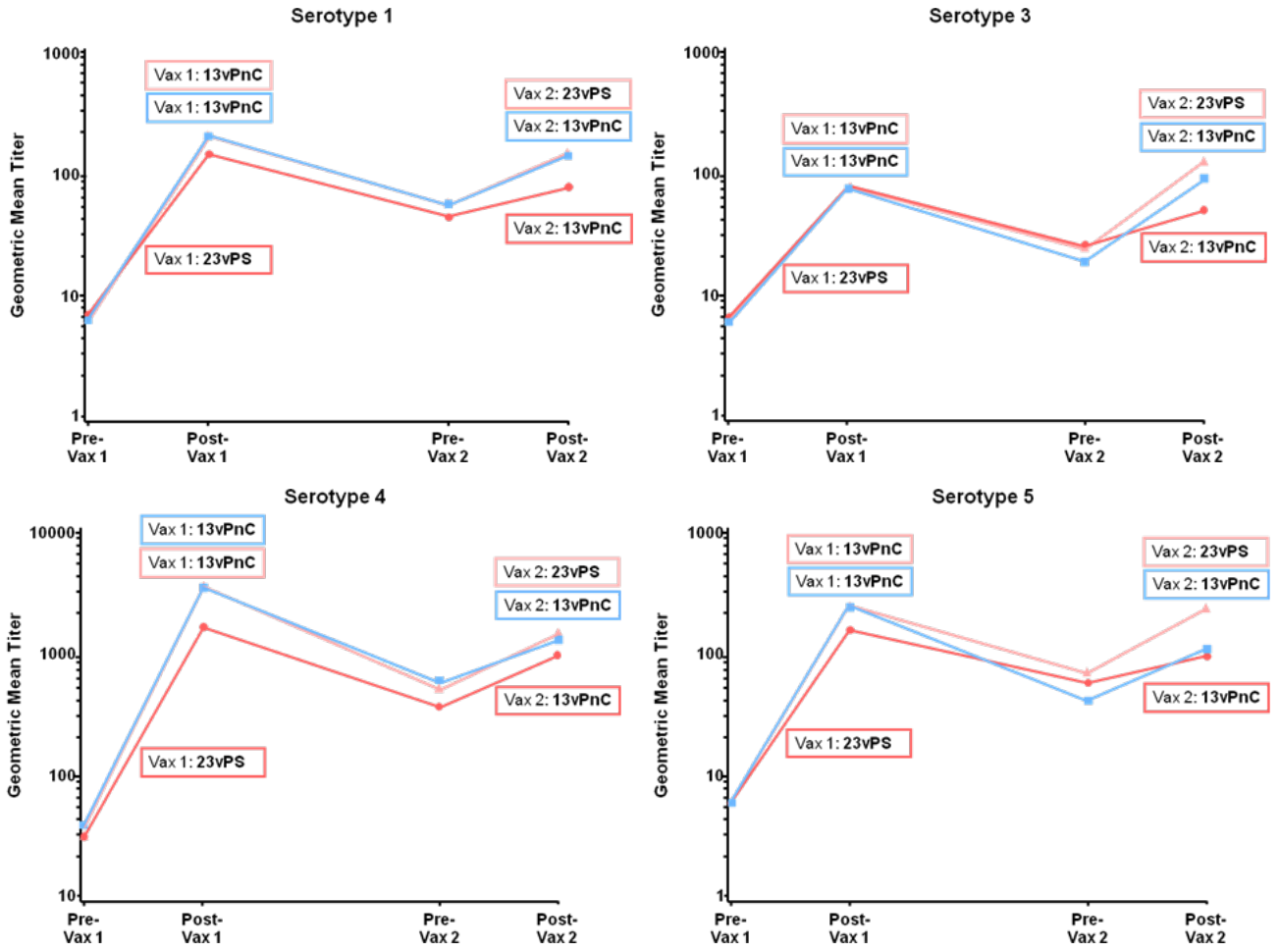


Figure 4-19: Study 3010 – Naïve Subjects 60-64 yo, OPA Antibody Response Curves, Serotypes 6A, 6B, 7F, 9V

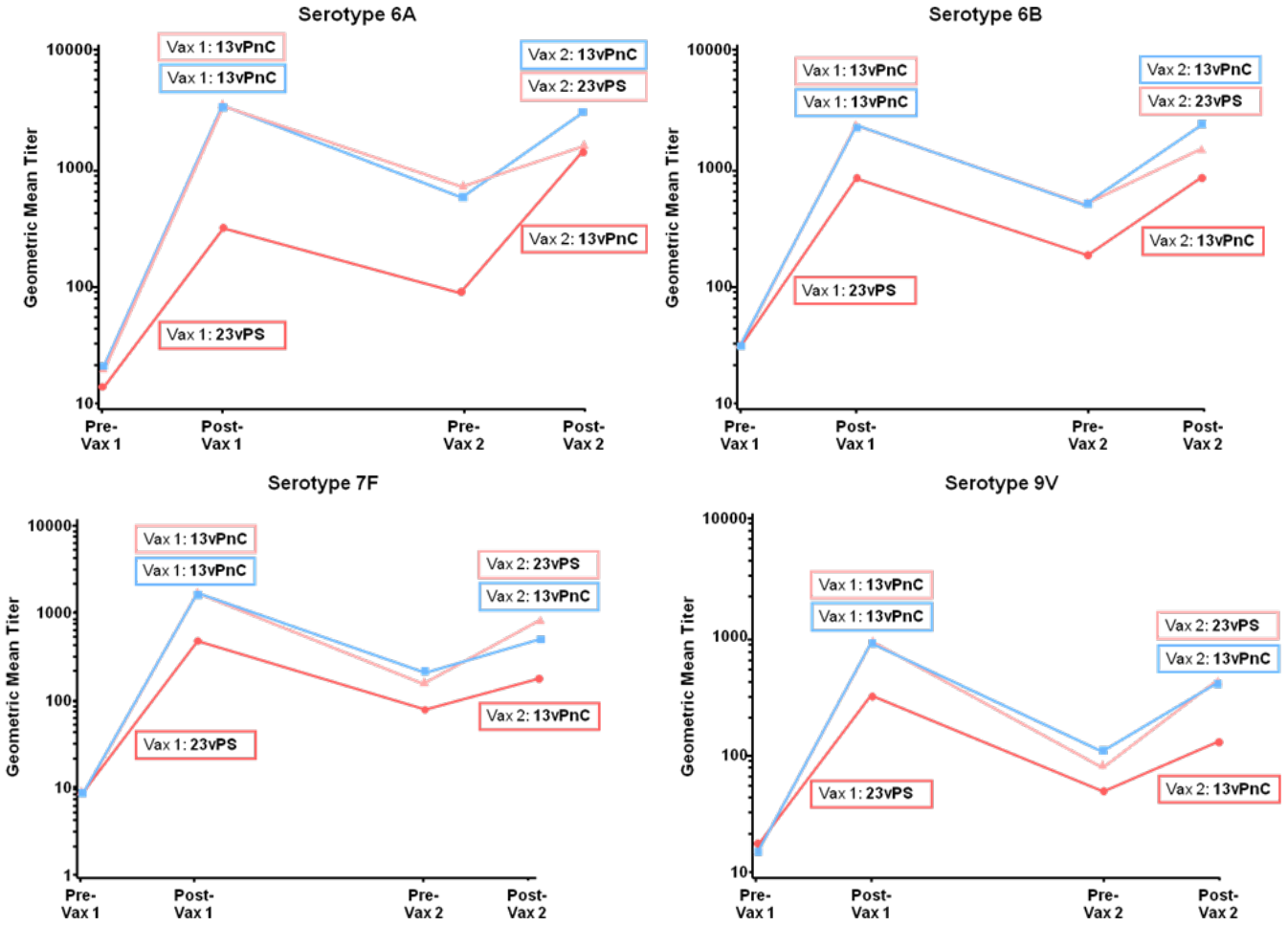


Figure 4-20: Study 3010 – Naïve Subjects 60-64 yo, OPA Antibody Response Curves, Serotypes 14, 18C, 19A, 19F

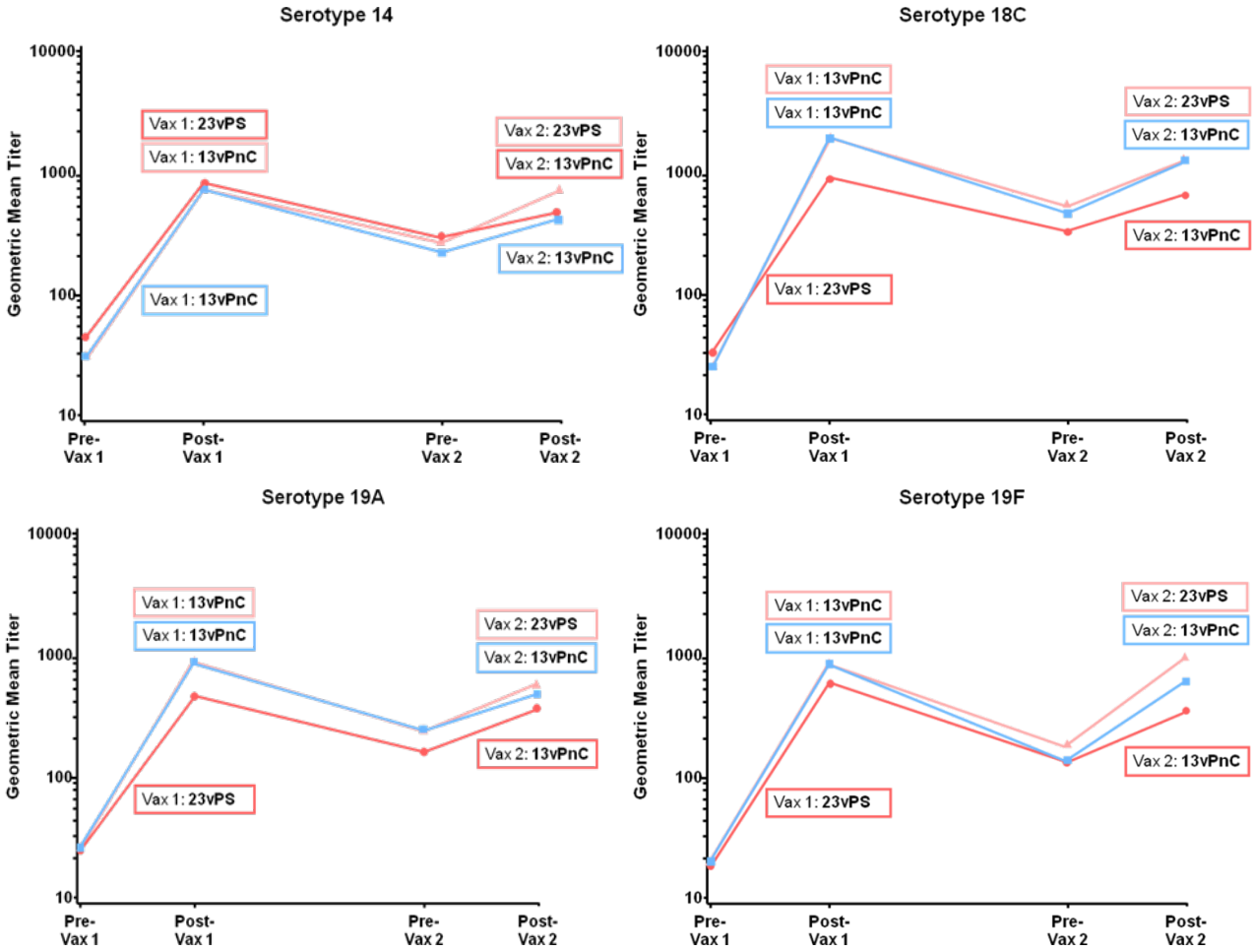
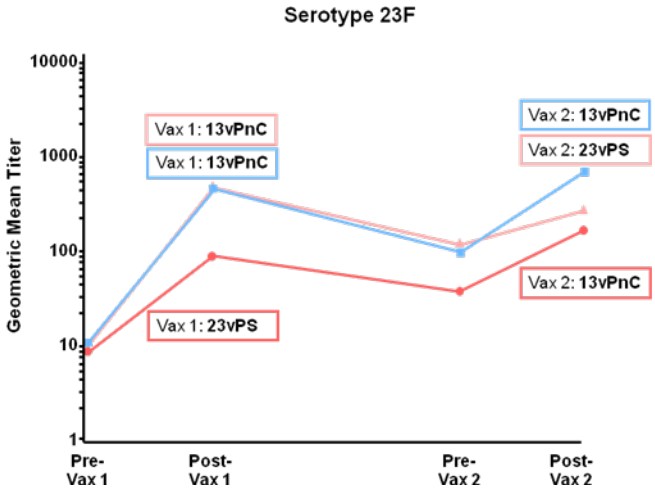


Figure 4-21: Study 3010 – Naïve Subjects 60-64 yo, OPA Antibody Response Curves, Serotype 23F



Based on the observations with sequential dosing at a 1-year interval in 3010, an open label extension of the 004 study was conducted in which the following sequences were investigated: 13vPnC/23vPS, 13vPnC/13vPnC, and 23vPS/23vPS, with a 3.5 to 4-year interval between doses. Evaluation of serologic responses remained blinded in this study extension.

The 004 extension study confirmed that (1) 13vPnC established immune memory to vaccine-associated pneumococcal polysaccharides in subsequent 23vPS, augmenting responses of 13vPnC/23vPS compared to 23vPS alone and restoring or statistically increasing 13vPnC/13vPnC responses compared to 13vPnC alone for the majority of serotypes, after a 3.5 to 4-year interval; (2) 13vPnC followed by 13vPnC over this longer interval resulted in recovery of the immune response for the large majority of serotypes, and increased OPA values for 7 of 13 sertoypes compared to the first dose, thus confirming the hypothesis that expanding the interval between vaccine doses would permit revaccination to extend protection; (3) 23vPS/23vPS was associated with uniform reductions in response after the second dose, indicating that establishment of memory and the potential to induce comparable antibody response after successive doses are not possible with 23vPS. The detailed results of the 004 extension study are presented in the following Section 4.5.5.

4.5.5 Key Immunogenicity Objectives and Results after 13PnC/23vPS, 13vPnC/13vPnC, or 23vPS/23vPS with a 3.5 to 4-Year Interval Between Doses, 004 Extension Study

The 004 open label extension study design is shown in Figure 4-22 (shaded). All second doses of vaccine were administered an average of 3.7 years after the first dose. This examination of the sequence 13vPnC/23vPS afforded the opportunity to confirm establishment of memory and improved response to 23vPS, with a longer interval between doses. The 13vPnC/13vPnC sequence permitted evaluation of the potential to recover and possibly improve response, with this longer interval between doses, as hypothesized based on the results from study 3010. Given the importance of determining the best approach to reimmunization, this extension afforded the opportunity to assess the impact of 23vPS on subsequent 23vPS, and the relative value of 13vPnC/13vPnC compared to 23vPS/23vPS. All serologic evaluations remained blinded for this analysis.

Figure 4-22: Study 004 Extension Cohort 1

Study Design				
Age	Cohort	N	Year 0	Year 3.5 to 4
60-64 yo Naive	1.1	370	13vPnC	13vPnC
				23vPS
	1.2	370	23vPS	23vPS
50-59 yo Naive	2	370	13vPnC	13vPnC

Study 004 extension met both primary objectives and their associated secondary objectives.

4.5.5.1 Evidence to Support That 13vPnC Establishes Immune Memory to 23vPS Administered 3.5 to 4 Years Later, Augmenting Antibody Response Compared to 23vPS Alone and Restoring or Statistically Increasing Response Compared to 13vPnC Alone for the Majority of Serotypes in Common, 004 Extension Study

The antibody responses to 23vPS administered 3 to 4 years after an initial dose of 13vPnC were compared to an initial dose of 23vPS in the 60 to 64-year-old age group as measured

by serotype-specific OPA geometric mean titers (GMTs) (13vPnC/23vPS versus 23vPS, 1st of two co-primary objectives).

The lower limit of the 95% CI for the GMRs exceeded 1.0 for 9 of 12 common serotypes, indicating a statistically significantly greater OPA response after 13vPnC/23vPS than after 23vPS (Table 4-16).

Table 4-16: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC/23vPS vs 23vPS (Objective of Primary Interest)

Serotype	13vPnC/23vPS GMT	23vPS GMT	GMT Ratio	(95% CI)
1	398	116	3.4	(2.32, 5.09)
3	164	105	1.6	(1.13, 2.16)
4	1875	1420	1.3	(0.88, 1.98)
5	476	149	3.2	(2.04, 4.97)
6B	2670	1088	2.5	(1.50, 4.00)
7F	1895	403	4.7	(2.76, 7.99)
9V	1089	654	1.7	(0.93, 2.97)
14	1268	824	1.5	(0.99, 2.39)
18C	2489	1135	2.2	(1.37, 3.50)
19A	966	377	2.6	(1.78, 3.68)
19F	1653	621	2.7	(1.77, 4.01)
23F	299	86	3.5	(1.99, 6.13)
6A	832	274	3.0	(1.61, 5.73)

- Non-inferiority met for all 12 common serotypes for 13vPnC/23vPS compared to 23vPS
- 9 of 12 common serotypes statistically significantly greater (lower limit of 95% CI >1.0) for 13vPnC/23vPS compared to 23vPS

Antibody responses to 23vPS administered 3 to 4 years after an initial dose of 13vPnC were compared to 23vPS administered 3 to 4 years after an initial dose of 23vPS in the 60 to 64-year-old age group as measured by serotype-specific OPA GMTs (13vPnC/23vPS versus 23vPS/23vPS; 2nd of two co-primary objectives).

After vaccination 2, 13vPnC/23vPS elicited statistically significantly greater OPA responses than 23vPS/23vPS for all 12 common serotypes and serotype 6A (Table 4-17).

Table 4-17: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC/23vPS vs 23vPS/23vPS (Objective of Coprimary Interest)

Serotype	13vPnC/23vPS GMT	23vPS/23vPS GMT	GMT Ratio	(95% CI)
1	398	95	4.2	(2.87, 6.08)
3	164	53	3.1	(2.26, 4.30)
4	1875	733	2.6	(1.72, 3.80)
5	476	74	6.5	(4.09, 10.19)
6A	832	123	6.8	(3.72, 12.33)
6B	2670	916	2.9	(1.83, 4.63)
7F	1895	497	3.8	(2.41, 6.03)
9V	1089	187	5.8	(3.13, 10.82)
14	1268	661	1.9	(1.30, 2.84)
18C	2489	802	3.1	(2.02, 4.78)
19A	966	364	2.7	(1.87, 3.76)
19F	1653	374	4.4	(2.97, 6.58)
23F	299	54	5.5	(3.20, 9.41)

- All 12 common serotypes and serotype 6A met non-inferiority
- Statistically significantly greater responses for all 12 common serotypes and serotype 6A after 13vPnC/23vPS compared to 23vPS/23vPS (lower 95%CI >1.0)

Within-group comparison of the vaccination 2 response versus the vaccination 1 response after 13vPnC/23vPS versus 13vPnC in cohort 1 (secondary objective).

OPA responses were similar or higher after 13vPnC/23vPS than after 13vPnC for most serotypes. The OPA GMTs were statistically significantly greater (GMFR CI lower limit exceeded 1.0) after 13vPnC/23vPS than after 13vPnC for 7 of the 12 common serotypes. OPA response was statistically significantly lower (GMFR CI upper limit less than 1) after 13vPnC/23vPS than after 13vPnC for 3 serotypes (4, 9V, 6A). These results show that for the majority of serotypes response to the initial 13vPnC dose is enhanced by a subsequent 23vPS

dose administered 3.5 to 4 years later, a finding consistent with induction of a memory response (Table 4-18).

Table 4-18: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC/23vPS vs 13vPnC

Serotype	13vPnC/23vPS GMT	13vPnC GMT	GMT Ratio	(95% CI)
1	377	172	2.2	(1.64, 2.94)
3	162	102	1.6	(1.23, 2.03)
4	1997	2894	0.7	(0.51, 0.94)
5	445	239	1.9	(1.37, 2.53)
6A	812	2884	0.3	(0.21, 0.37)
6B	2707	2664	1.0	(0.79, 1.31)
7F	1818	971	1.9	(1.25, 2.80)
9V	909	1474	0.6	(0.42, 0.91)
14	1367	655	2.1	(1.43, 3.04)
18C	2503	2136	1.2	(0.92, 1.49)
19A	967	765	1.3	(1.05, 1.55)
19F	1670	675	2.5	(1.69, 3.61)
23F	333	432	0.8	(0.56, 1.07)

- For 7 of the 12 common serotypes statistically significantly greater responses for 13vPnC/23vPS compared to 13vPnC
- For 2 of 12 common serotypes and 6A statistically significantly lower responses after 13vPnC/23vPS compared to 13vPnC

Note: For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.

13vPnC induces a memory response to subsequently administered 23vPS for the vaccine serotype-specific polysaccharides as demonstrated by an increase in antibody responses after 13vPnC/23vPS compared to 23vPS alone or 13vPnC alone; the increase observed with a 1-year interval between doses (study 3010) is even more pronounced after an interval of 3.5 to 4 years (004 extension), in the latter case even exceeding the first dose of 13vPnC for the majority of serotypes. This is very different than the reduced response seen after the 23vPS/13vPnC sequence (study 3010) or 23vPS/23vPS sequence (004 extension) and confirms that 13vPnC is the preferred first choice for immunization of naïve adults to optimize antibody response, induction of memory, and maintenance of long-term protection.

4.5.5.2 Evidence to Support That 13vPnC Establishes Immune Memory to 13vPnC Administered 3.5 to 4 Years Later, Augmenting Antibody Response Compared to 13vPnC Alone for the Majority of Serotypes, and Permitting a Strategy of Revaccination at an Appropriately Defined Interval, 004 Extension Study

As shown in study 3010, statistically significantly lower OPA responses were observed for the majority of serotypes after vaccination 2 of the sequence 13vPnC/13vPnC than after the initial 13vPnC dose, with an interval of 1 year between doses. Because high circulating antibody titers following initial 13vPnC vaccination might interfere with response to subsequent vaccination when the interval between doses is short, the 004 extension study investigated whether extending the interval to 3.5 to 4 years would result in greater response to second dose of 13vPnC. In the 004 extension study, response to 13vPnC/13vPnC was evaluated relative to an initial 13vPnC dose in cohort 1 and cohort 2, and relative to the sequences 13vPnC/23vPS and 23vPS/23vPS in cohort 1.

Within-group comparison of the vaccination 2 response versus the vaccination 1 response were performed for subjects in the 13vPnC/13vPnC vaccine sequence in both cohorts 1 and 2: 13vPnC/13vPnC versus 13vPnC (secondary objective).

In contrast to observations after 1 year in study 3010, OPA GMTs for cohort 1 were similar or statistically significantly higher (7 of 13 serotypes) after 13vPnC/13vPnC than after the initial 13vPnC dose as evaluated by GMFRs between doses (Table 4-19). The lower limit of the 95% CI for the GMFR was greater than 0.5 for all but 1 serotype (9V).

Table 4-19: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC/13vPnC vs 13vPnC

Serotype	13vPnC/13vPnC GMT	13vPnC GMT	GMT Ratio	(95% CI)
1	334	155	2.2	(1.59, 2.92)
3	87	102	0.9	(0.68, 1.08)
4	1194	1626	0.7	(0.53, 1.01)
5	277	180	1.5	(1.09, 2.16)
6A	2126	2411	0.9	(0.64, 1.21)
6B	4357	2312	1.9	(1.42, 2.50)
7F	1226	928	1.3	(0.89, 1.95)
9V	855	1163	0.7	(0.46, 1.17)
14	1040	746	1.4	(1.01, 1.93)
18C	1837	1529	1.2	(0.93, 1.55)
19A	791	591	1.3	(1.06, 1.68)
19F	989	467	2.1	(1.48, 3.04)
23F	918	448	2.1	(1.40, 3.01)

- **7 of 13 serotypes statistically significantly greater responses for 13vPnC/13vPnC compared to 13vPnC**

Note: For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.

OPA GMTs for cohort 2 after 13vPnC/13vPnC were similar or statistically significantly higher (6 of 13 serotypes) compared to responses after the initial dose of 13vPnC for most serotypes. The lower limit of the 95% CI for the GMFR was greater than 0.5 for all serotypes except serotype 4 (95% CI: 0.49, 0.73). Antibody responses for 3 serotypes (4, 6A, 9V) were statistically significantly lower after the second 13vPnC dose (Table 4-20). When OPA responses after 13vPnC/13vPnC were compared in cohorts 1 and 2, responses were similar for most serotypes in the 2 cohorts.

Table 4-20: Study 004 (Ext) – Naïve Subjects 50-59 yo, OPA GMTs 13vPnC/13vPnC vs 13vPnC

Serotype	13vPnC/13vPnC GMT	13vPnC GMT	GMT Ratio	(95% CI)
1	296	198	1.5	(1.20, 1.86)
3	85	91	0.9	(0.80, 1.08)
4	1685	2817	0.6	(0.49, 0.73)
5	291	235	1.2	(1.02, 1.50)
6A	3143	4347	0.7	(0.60, 0.87)
6B	4886	3085	1.6	(1.29, 1.95)
7F	1659	1596	1.0	(0.83, 1.30)
9V	1492	1933	0.8	(0.61, 0.98)
14	1278	865	1.5	(1.15, 1.90)
18C	2156	1742	1.2	(0.96, 1.59)
19A	1048	959	1.1	(0.94, 1.27)
19F	1182	633	1.9	(1.51, 2.32)
23F	1188	563	2.1	(1.63, 2.73)

- 6 of 13 serotypes statistically significantly greater responses for 13vPnC/13vPnC compared to 13vPnC

Note: For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.

The restoration or improvement in antibody response seen after a second dose in the 13vPnC/13vPnC sequence, contrasts markedly with the negative response seen for the antibody response to the second dose after 23vPS/23vPS, as evaluated in the following objective.

Within-group comparison of the vaccination 2 response versus the vaccination 1 response for subjects in the 23vPS/23vPS vaccine sequence: 23vPS/23vPS versus 23vPS for subjects in cohort 1 (secondary objective).

The within-group comparison of the vaccination 2 response versus the vaccination 1 response for subjects in the 23vPS/23vPS vaccine sequence (23vPS/23vPS versus 23vPS) is summarized in Table 4-21. The lower limit of the 95% CI for the GMFR was greater than 0.5 for 7 of the 12

common serotypes: 1, 6B, 7F, 14, 18C, 19A, and 19F. The upper limit of the 95% CI for the GMFRs was less than 1.0, indicating that the OPA response was statistically significantly lower after 23vPS/23vPS than after 23vPS for 8 of the 12 common serotypes: 3, 4, 5, 9V, 14, 18C, 19F, and 23F and serotype 6A. The serotype-specific GMFRs ranged from 0.3 (serotype 9V) to 1.1 (serotype 7F) with only 1 serotype greater than 1 (serotype 7F). In summary, these results indicate a statistically significantly diminished antibody response after the second dose of 23vPS compared to the initial dose.

Table 4-21: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA GMTs 23vPS/23vPS vs 23vPS

Serotype	23vPS/23vPS GMT	23vPS GMT	GMT Ratio	(95% CI)
1	95	115	0.8	(0.68, 1.02)
3	53	103	0.5	(0.44, 0.59)
4	725	1437	0.5	(0.40, 0.64)
5	71	152	0.5	(0.39, 0.56)
6B	915	1133	0.8	(0.62, 1.04)
7F	466	440	1.1	(0.81, 1.37)
9V	181	669	0.3	(0.18, 0.41)
14	619	823	0.8	(0.60, 0.95)
18C	822	1096	0.8	(0.60, 0.94)
19A	361	374	1.0	(0.83, 1.12)
19F	405	596	0.7	(0.57, 0.81)
23F	56	91	0.6	(0.50, 0.76)
6A	133	286	0.5	(0.35, 0.62)

- 8 of 12 common serotypes statistically significantly lower responses for 23vPS/23vPS compared to 23vPS
- For 5 of 12 common serotypes lower 95% CI ≤0.5 for 23vPS/23vPS compared to 23vPS

Note: For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.

The dramatic nature of the difference in potential for revaccination to maintain optimum antibody response is best evidenced by direct comparison of the 13vPnC/13vPnC to the 23vPS/23vPS sequence (secondary objective).

Comparisons of vaccination 2 responses after the vaccine sequence 13vPnC/13vPnC versus the 23vPS/23vPS sequence for subjects in cohort 1 (secondary objective).

The OPA response was statistically significantly greater (lower limit of CI for ratio >1) after 13vPnC/13vPnC than after 23vPS/23vPS for all serotypes, and the 95% lower CI was greater than 2, or statistically superior, for 6 of 13 serotypes (Table 4-22).

Table 4-22: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA GMTs 13vPnC/13vPnC vs 23vPS/23vPS

Serotype	13vPnC/13vPnC GMT	23vPS/23vPS GMT	GMT Ratio	(95% CI)
1	334	95	3.5	(2.39, 5.14)
3	87	53	1.6	(1.19, 2.28)
4	1175	733	1.6	(1.05, 2.44)
5	276	74	3.7	(2.32, 6.04)
6B	4184	916	4.6	(2.92, 7.15)
7F	1223	497	2.5	(1.56, 3.89)
9V	770	187	4.1	(2.22, 7.65)
14	1031	661	1.6	(1.07, 2.26)
18C	1918	802	2.4	(1.54, 3.72)
19A	789	364	2.2	(1.52, 3.08)
19F	958	374	2.6	(1.68, 3.92)
23F	867	54	15.9	(9.33, 27.19)
6A	2064	123	16.8	(9.45, 29.87)

- 12 of 12 common serotypes statistically significantly greater after 13vPnC/13vPnC compared to 23vPS/23vPS

Findings are consistent with establishment of memory response after a first dose of 13vPnC and the ability to revaccinate with 13vPnC to maintain optimum antibody response, not achievable with 23vPS.

Figure 4-23 to Figure 4-26 display plots of 13vPnC/23vPS, 13vPnC/13vPnC, and 23vPS/23vPS from cohort 1 originally immunized at 60 to 64 years of age.

Figure 4-23: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA Antibody Response Curves, Serotypes 1, 3, 4, 5

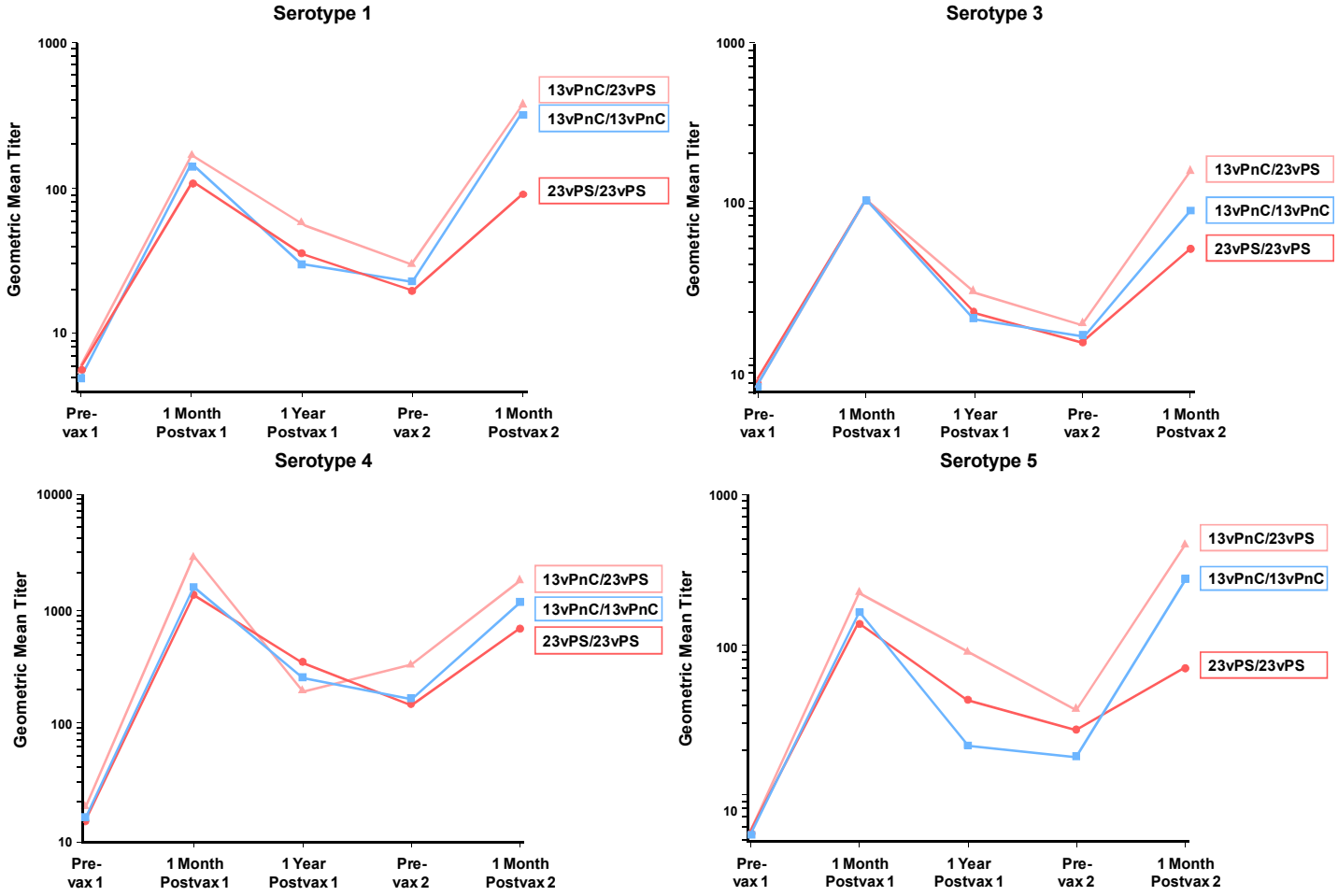


Figure 4-24: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA Antibody Response Curves, Serotypes 6A, 6B, 7F, 9V

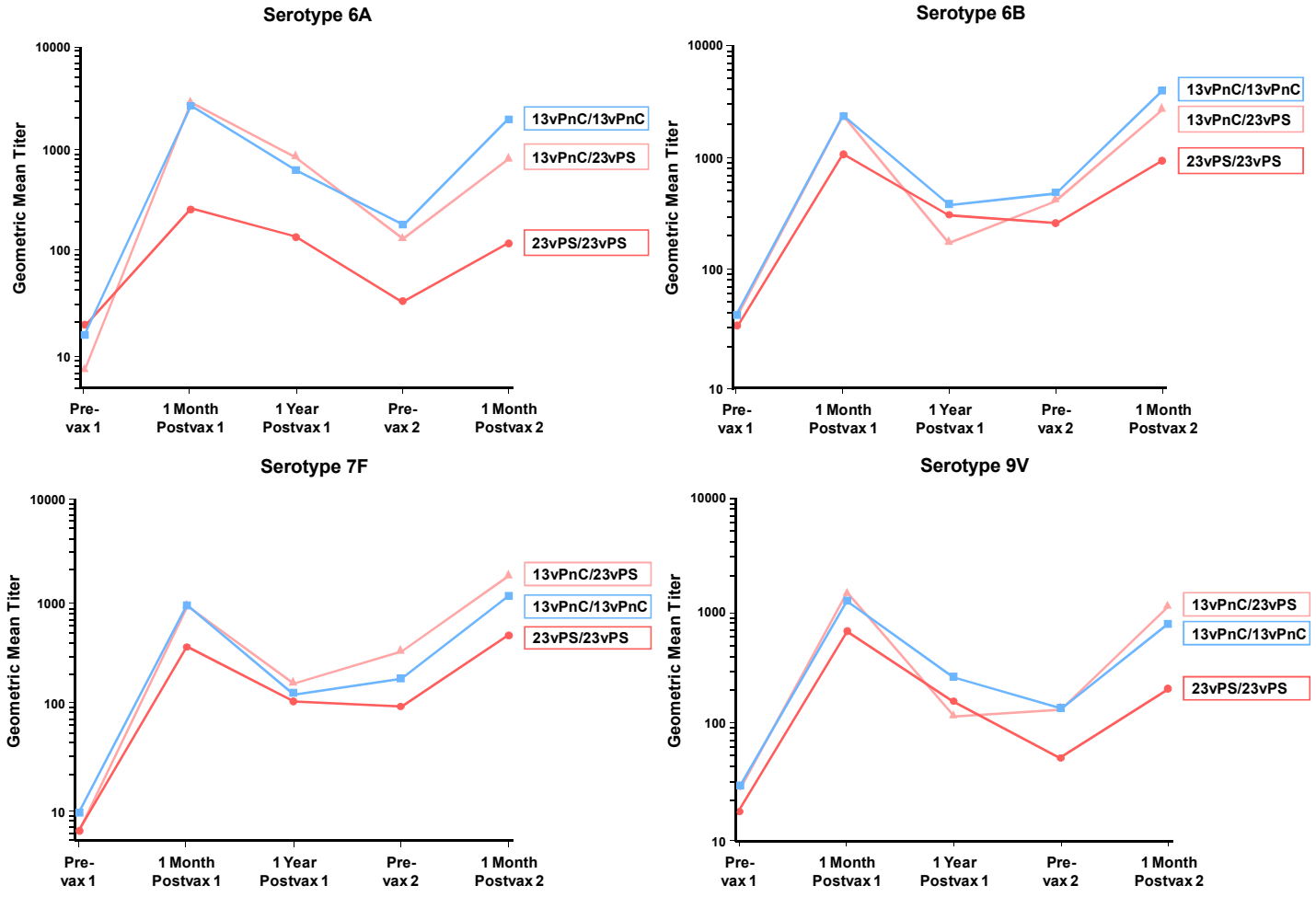


Figure 4-25: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA Antibody Response Curves, Serotypes 14, 18C, 19A, 19F

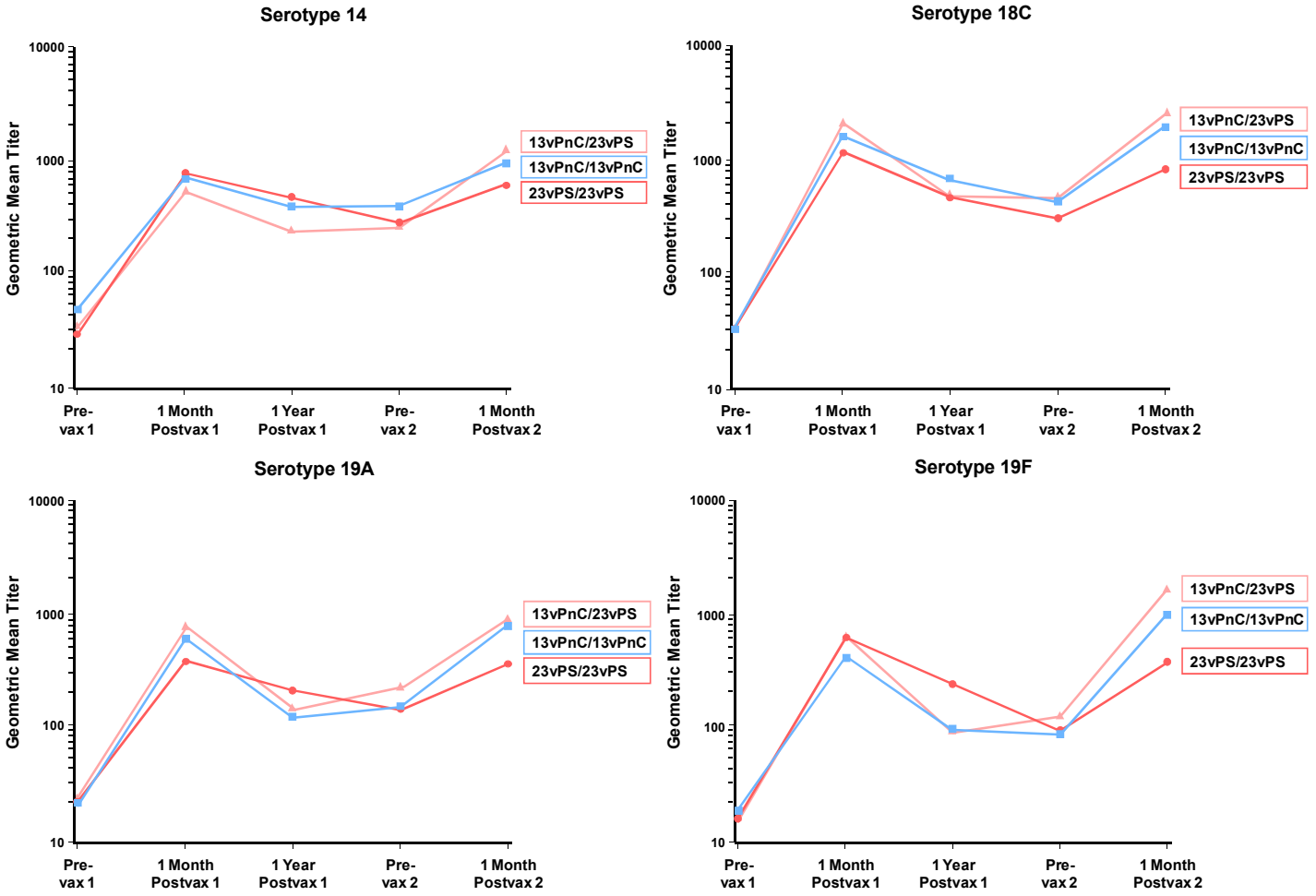
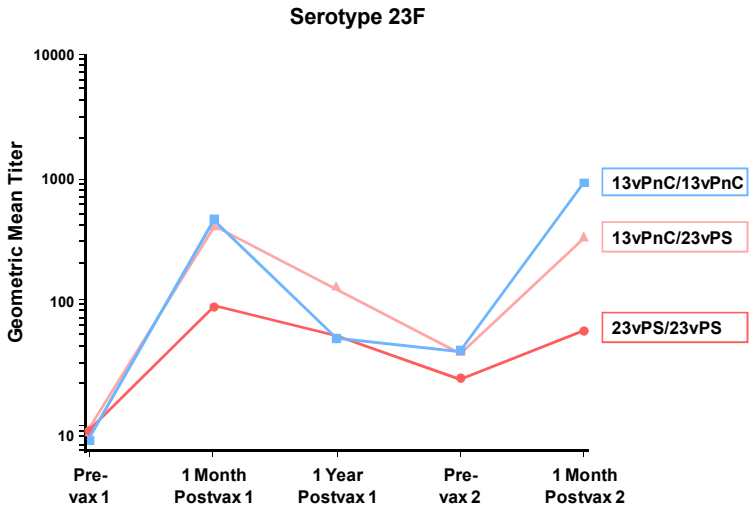


Figure 4-26: Study 004 (Ext) – Naïve Subjects 60-64 yo, OPA Antibody Response Curves, Serotype 23F



4.5.6 Conclusions Regarding Sequential Administration of 2 Doses of 13vPnC, 004 Extension Study

In pneumococcal vaccine-naïve adults, 13vPnC elicited an antibody response to subsequent 23vPS, administered 3.5 to 4 years later, that was generally statistically greater than that of 23vPS administered alone and comparable or statistically greater for nearly all serotypes compared to a first dose of 13vPnC. A second dose of 13vPnC 3.5 to 4 years after the first (13vPnC/13vPnC), restored antibody titers to previous levels for nearly all serotypes, and induced higher antibody responses for the majority compared to responses after the first dose. This contrasts with the lower responses seen after a 1-year dosing interval. Findings indicate that antibody responses can be restored, and even improved with a longer interval between the initial 13vPnC dose and a subsequent 23vPS dose or 13vPnC dose. 13vPnC/13vPnC responses were uniformly higher than those after 23vPS/23vPS, statistically so for all, and with 95% lower CIs >2 for 6 serotypes, indicating superior antibody responses. This has important implications for a vaccine strategy designed to optimize potential for memory and long-term protection by revaccination. In contrast to the inability of 23vPS to establish memory or restore antibody response by revaccination, 13vPnC establishes memory and permits revaccination after 3.5 to 4 years to maintain and often increase antibody titers to optimize protection for the lifetime of

risk. These data indicate that it is now possible to maintain immune response against pneumococcus for an extended period, when 13vPnC is given as the first vaccine to pneumococcal vaccine-naïve subjects. Additional data will be included in a later submission to more completely define appropriate timing of a second dose.

4.6 Evaluation of Concomitant Administration of 13vPnC and Trivalent Inactivated Influenza Vaccine (TIV), Studies 3001 and 3008

4.6.1 Concomitant Administration of 13vPnC and TIV in Adults 50 to 59 Years of Age, Study 3001

The ability to administer 13vPnC vaccine at an annual visit for influenza vaccination is desirable from both a convenience and public health perspective to encourage compliance with immunization. Therefore, the 3001 study evaluated the safety, tolerability, and immunogenicity data of 13vPnC when administered concomitantly with US-licensed trivalent inactivated influenza vaccine (TIV) in adults 50 to 59 years of age who were naïve to 23vPS. In addition, data on the kinetics of the immune response to the serotypes in 13vPnC at yearly intervals over a 5-year period will be evaluated, but is not part of this submission. This study will also allow assessment of the recall response to a second dose of 13vPnC given 5 years after the initial dose. This submission presents data from the initial part of the study only, referred to as year 0. It includes the period from study start (signing of the informed consent form [ICF]), through the 1-month postdose 2 blood draw, and a 6-month follow-up telephone contact. Follow-up data from years 1 through 5 will be presented in a subsequent report. The design of study 3001 is shown in Figure 4-27.

Figure 4-27: Study 3001 Design

Study Design					
		For Licensure		Post Licensure	
Group	N	Year 0	1 Month	Year 1-4	Year 5
1	550	TIV+13vPnC	Placebo	Annual Bleeds	13vPnC
2	550	TIV+Placebo	13vPnC		13vPnC

4.6.1.1 Summary of Immunogenicity Objectives and Results, Study 3001

The 2 coprimary objectives of this study were achieved.

The immune responses induced by TIV when administered concomitantly with 13vPnC are non-inferior to the immune responses induced by TIV alone, as measured by the standard hemagglutination inhibition assay (HAI) for the A/H1N1, A/H3N2, and B vaccine strains, 1 month after vaccination with TIV (1st of two coprimary objectives). Non-inferiority was met for all 3 strains of TIV; the lower limits of the 95% CIs for the difference in proportions of responders were greater than -10% (Table 4-23).

Table 4-23: Study 3001 – Naïve Subjects 50-59 yo, ≥4-Fold Increase in HAI Titer 13vPnC+TIV vs TIV+Placebo

Percent of Subjects Achieving a ≥4-Fold Increase in Titer After Dose 1

TIV: HAIs	TIV + 13vPnC (%)	TIV + Placebo (%)	Difference	(95% CI)
A/H1N1	84.0	81.2	2.8	(-1.8, 7.4)
A/H3N2	71.1	69.5	1.6	(-3.9, 7.2)
B	60.6	60.3	0.3	(-5.6, 6.2)

- Pre-defined non-inferiority criteria were met for all TIV strains

The marginal failure of the concomitant 13vPnC+TIV group to meet the FDA guidance[152] for subjects achieving an antibody titer >40 for the B strain was at least partly due to the overall poor immunogenicity of the B/Malaysia/2506/2004 in this population. The same vaccine containing the same influenza B vaccine antigen achieved somewhat higher antibody responses in an older European population and the criterion was met when TIV and 13vPnC were administered concomitantly in this group (see Section 4.6.2).

Immune responses to the 13vPnC serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 13vPnC when administered concomitantly with TIV (13vPnC+TIV) are non-inferior to the immune responses induced by 13vPnC administered 1 month after TIV, as measured by serotype-specific immunoglobulin G (IgG) concentrations 1 month after initial vaccination with 13vPnC in a subset of subjects (2nd of two coprimary objectives). The non-inferiority criterion (ie, a lower limit of the 2-sided 95% CI for the GMR of >0.5) was met for all serotypes (Table 4-24).

Table 4-24: Study 3001 – Naïve Subjects 50-59 yo, IgG GMCs (µg/mL)
13vPnC+TIV vs 13vPnC

Serotype	13vPnC+TIV GMC	13vPnC GMC	Ratio	(95% CI)
1	4.05	5.45	0.74	(0.58, 0.95)
3	1.15	1.46	0.79	(0.66, 0.93)
4	2.35	3.41	0.69	(0.55, 0.87)
5	6.03	7.18	0.84	(0.67, 1.05)
6A	5.78	6.70	0.86	(0.70, 1.06)
6B	7.58	10.09	0.75	(0.60, 0.93)
7F	8.14	10.57	0.77	(0.63, 0.95)
9V	4.96	6.97	0.71	(0.59, 0.86)
14	10.77	14.05	0.77	(0.60, 0.98)
18C	9.65	13.49	0.72	(0.58, 0.88)
19A	16.80	18.84	0.89	(0.74, 1.08)
19F	6.13	7.13	0.86	(0.67, 1.10)
23F	7.17	8.54	0.84	(0.66, 1.08)

- **Non-inferiority criterion met for all serotypes**

Given the lower IgG point estimates after concomitant 13vPnC and TIV (statistically lower for 8 serotypes), and the acknowledged importance of OPA response in assessing potential for protection, a post-hoc analysis of OPA responses was performed in a random subset of subjects in each arm of this study (Table 4-25). OPA responses 1 month after administration of 13vPnC+TIV were statistically lower for 10 of 13 serotypes, with 95% lower CI for the ratio of <0.5 for 5 serotypes. The 95% CI of proportion of subjects with OPA responses ≥LLOQ overlapped for all serotypes, except serotype 5 (Table 4-26).

Table 4-25: Study 3001 – Naïve Subjects 50-59 yo, OPA GMTs 13vPnC+TIV vs 13vPnC

Serotype	13vPnC+TIV GMT (N=268-289)	13vPnC GMT (N=274-289)	Ratio	(95% CI)
1	150	264	0.6	(0.43, 0.75)
3	61	78	0.8	(0.63, 0.98)
4	1657	2203	0.8	(0.60, 0.95)
5	100	204	0.5	(0.35, 0.69)
6A	2160	3157	0.7	(0.51, 0.91)
6B	2421	3215	0.8	(0.57, 1.00)
7F	1584	2691	0.6	(0.43, 0.80)
9V	1053	1749	0.6	(0.43, 0.85)
14	1020	1554	0.7	(0.51, 0.85)
18C	1440	1978	0.7	(0.53, 1.00)
19A	777	1022	0.8	(0.61, 0.95)
19F	379	625	0.6	(0.43, 0.85)
23F	382	483	0.8	(0.54, 1.16)

- Non-inferiority criterion met for 8 of 13 serotypes (Missed NI for ST 1, 5, 7F, 9V, 19F)
- 13vPnC + TIV statistically significantly lower for 10 serotypes (ST 1, 3, 4, 5, 6A, 7F, 9V, 14, 19A, 19F)

Table 4-26: Study 3001 – Naïve Subjects 50-59 yo, OPA Titer ≥ LLOQ 13vPnC+TIV vs 13vPnC

Serotype	13vPnC+TIV %	13vPnC %	Difference	(95% CI)
1	88.9	94.0	-5.1	(-9.9, -0.4)
3	88.2	91.2	-3.0	(-8.2, 2.1)
4	97.5	98.2	-0.7	(-3.5, 1.9)
5	74.0	86.8	-12.8	(-19.4, -6.2)
6A	96.1	96.9	-0.8	(-4.1, 2.4)
6B	96.4	96.5	-0.1	(-3.4, 3.2)
7F	92.5	96.1	-3.5	(-7.7, 0.4)
9V	88.4	92.6	-4.2	(-9.2, 0.6)
14	96.1	97.2	-1.0	(-4.3, 2.1)
18C	93.5	94.7	-1.2	(-5.3, 2.8)
19A	98.2	98.6	-0.3	(-2.8, 2.1)
19F	88.0	91.5	-3.5	(-8.7, 1.5)
23F	84.5	86.1	-1.6	(-7.6, 4.3)

•Lower 95% CI for the difference between groups was >-10.0 for most serotypes

4.6.1.2 Overall Immunogenicity Conclusions, Study 3001

13vPnC and US-licensed TIV are immunologically compatible when administered together. The proportions of responders who had a ≥4-fold increase in HAI titer for TIV vaccine antigens were similar after 13vPnC+TIV and placebo+TIV (dose 1, groups 1 and 2, respectively). The predefined non-inferiority criterion (ie, lower limit of the 95% CI for the difference in proportion of responders >-10%) was met for all 3 antigens in TIV.

Comparison of pneumococcal IgG GMCs measured 1 month after 13vPnC+TIV (dose 1) relative to 1 month after 13vPnC alone (dose 2) in groups 1 and 2, respectively, showed that the predefined non-inferiority criterion (ie, the lower limit of the 2-sided 95% CI for the geometric

mean ratio of >0.5) was met for all serotypes. However, when 13vPnC was given concomitantly with TIV, IgG GMC and OPA GMT responses to 13vPnC were lower for most serotypes compared to responses when 13vPnC was given alone.

4.6.2 Concomitant Administration of 13vPnC and TIV in Adults ≥65 Years of Age, Study 3008

As for study 3001, conducted in the United States, the 3008 study evaluated the immunologic compatibility of 13vPnC and TIV when coadministered, but in an older population of Europeans. The ability to coadminister both vaccines at a single visit would likely improve compliance and better serve public health. The 3008 study evaluated the safety, tolerability, and immunogenicity data of 13vPnC when administered concomitantly with TIV in adults 65 years of age or older who were naïve to 23vPS. The design of study 3008 is shown in Figure 4-28.

Figure 4-28: Study 3008 Design

Study Design			
Group	**N**	**Year 0**	**1 Month**
1	**550**	**TIV+13vPnC**	**Placebo**
2	**550**	**TIV+Placebo**	**13vPnC**

4.6.2.1 Summary of Immunogenicity Objectives and Results, Study 3008

Evaluation of the coprimary objectives revealed results similar to those of younger adults in the 3001 study and are summarized here:

The immune responses induced by TIV when administered concomitantly with 13vPnC are non-inferior to the immune responses induced by TIV alone as measured by the standard HAIs for the A/H1N1 and B vaccine strains 1 month after vaccination with TIV, but missed meeting the pre-established criteria for H3N2 by a small margin (1st of two coprimary objectives). Non-inferiority was met for A/H1N1 and B. For A/H3N2, the difference in proportion of responders (ie, 58.0% for 13vPnC+TIV - 62.6% for TIV+placebo) was -4.6%, with

a lower limit of the 95% CI of -10.4% (ie, slightly lower than the predefined non-inferiority criterion of >-10%; Table 4-27).

Table 4-27: Study 3008 – Naïve Subjects ≥65 yo, ≥4-Fold Increase in HAI Titer 13vPnC+TIV vs TIV+Placebo

Percent of Subjects Achieving a ≥4-Fold Increase in TIV Titer After Dose 1

	13vPnC+TIV/Placebo (%)	Placebo+TIV/13vPnC (%)	Difference	(95% CI)
TIV: HAIs				
A/H1N1	80.3	78.6	1.7	(-3.1, 6.5)
A/H3N2	58.0	62.6	-4.6	(-10.4, 1.3)
B	52.2	54.0	-1.8	(-7.8, 4.1)

- **Met non-inferiority criterion for HAI, except A/H3N2 that missed by a small margin at the 95% LCI**
- **FDA Guidance for seasonal flu vaccine:**
  - **The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HAI antibody exceeded 30% for all 3 strains**
  - **The lower bound of the two-sided 95% CI for the percent of subjects achieving an HAI antibody titer >1:40 exceeded 60% for all 3 strains**

As a post-hoc analysis, all criteria proposed in the FDA guidance for seasonal trivalent inactivated influenza vaccine (TIV) were exceeded for all 3 influenza antigens when TIV was coadministered with 13vPnC. After dose 1, for the proportions of seroconversions (responders) in group 1 (13vPnC+TIV/placebo) and group 2 (TIV+placebo/13vPnC), the lower limit of the 95% CI exceeded the FDA guidance value of 30% for all 3 strains. The FDA guideline that the lower bound of the 2-sided 95% CI of subjects achieving HAI antibody titer ≥40 be ≥60% for adults over 65 years of age was met by the 3 strains. Hence, although the H3N2 response, after concomitant administration of TIV with 13vPnC, barely missed the non-inferiority criterion (-10.4%), the proportion of subjects with HAI titers >40 associated with protection was high (96.5%) and within 1% of values in subjects who received TIV alone (97.4%). The observed

higher preimmunization and postimmunization titers against H3N2 were likely related to more recent exposure to matching H3N2 strains in recent epidemics.

The immune responses to the 13vPnC serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, and 23F) induced by 13vPnC when administered concomitantly with TIV are non-inferior to the immune responses induced by 13vPnC administered 1 month after vaccination with TIV but missed non-inferiority for 19F by a small margin, as measured by serotype-specific immunoglobulin G (IgG) antibody concentrations in a subset of subjects (2nd of two coprimary objectives). The non-inferiority criterion (ie, a lower limit of the 2-sided 95% CI for the ratio of >0.5) was met for all serotypes, except for 19F. The IgG GMC for serotype 19F was 4.78 µg/mL when 13vPnC was administered concomitantly with TIV, and 7.39 µg/mL when administered alone; the lower limit of the 95% CI of the geometric mean ratio for 19F was 0.49 in the evaluable population (Table 4-28).

Table 4-28: Study 3008 – Naïve Subjects ≥65 yo, IgG GMCs (µg/mL) 13vPnC+TIV vs 13vPnC

Serotype	13vPnC+TIV GMC	13vPnC GMC	Ratio	(95% CI)
1	2.52	3.20	0.79	(0.60, 1.04)
3	1.08	1.15	0.94	(0.78, 1.13)
4	2.15	3.24	0.66	(0.51, 0.87)
5	4.74	6.90	0.69	(0.55, 0.86)
6A	4.61	6.10	0.76	(0.61, 0.94)
6B	6.24	6.43	0.97	(0.75, 1.25)
7F	7.63	9.04	0.84	(0.67, 1.07)
9V	4.97	6.21	0.80	(0.63, 1.02)
14	8.95	12.44	0.72	(0.53, 0.97)
18C	8.88	11.07	0.80	(0.64, 1.01)
19A	11.93	17.10	0.70	(0.56, 0.87)
19F	4.78	7.39	0.65	(0.49, 0.85)
23F	5.82	6.11	0.95	(0.71, 1.27)

- Non-inferiority criterion met for all serotypes except 19F

Given the lower IgG point estimates after concomitant 13vPnC and TIV (statistically lower for 6 serotypes), and the acknowledged importance of OPA response in assessing potential for protection, a post-hoc analysis of OPA responses was performed in a random subset of subjects in each arm of this study. OPA responses 1 month after administration of 13vPnC+TIV were statistically lower for 1 of 13 serotypes (serotype 4), with 95% lower CI <0.5 for 3 serotypes (4, 7F, 9V, Table 4-29). The 95% CIs for the proportion of subjects with serotype-specific OPA responses ≥LLOQ overlapped after 13vPnC+TIV compared with 13vPnC given alone and the lower 95% CI for the difference between groups was >-10.0 for most serotypes (exceptions 7F [-10.3] and 9V [-10.2], Table 4-30). When examined by age group subsets (ages 65 to 69, 70 to 74, 75 to 79, ≥80) the 95% CIs for the 2 groups overlapped for each serotype in each age subset.

Table 4-29: Study 3008 – Naïve Subjects ≥65 yo, OPA GMTs 13vPnC+TIV vs 13vPnC

Serotype	13vPnC+TIV GMT (N=235-236)	13vPnC GMT (N=234-255)	GMT Ratio	(95% CI)
1	88	95	0.9	(0.68, 1.24)
3	46	51	0.9	(0.69, 1.20)
4	997	1486	0.7	(0.47, 0.95)
5	124	112	1.1	(0.77, 1.60)
6A	1220	1597	0.8	(0.54, 1.08)
6B	1564	2017	0.8	(0.55, 1.09)
7F	607	835	0.7	(0.47, 1.12)
9V	477	723	0.7	(0.42, 1.03)
14	975	1088	0.9	(0.65, 1.24)
18C	1158	1415	0.8	(0.59, 1.14)
19A	445	539	0.8	(0.61, 1.12)
19F	378	467	0.8	(0.57, 1.16)
23F	245	295	0.8	(0.54, 1.27)

- Non-inferiority criteria met for 10 of 13 serotypes (exceptions ST 4, 7F, 9V)
- 13vPnC + TIV statistically significantly lower for 1 serotype (ST 4)

Table 4-30: Study 3008 – Naïve Subjects ≥65 yo, OPA Titer ≥ LLOQ
13vPnC+TIV vs 13vPnC

Serotype	13vPnC+TIV %	13vPnC %	Difference	(95% CI)
1	85.2	85.1	0.1	(-6.2, 6.3)
3	79.6	81.4	-1.9	(-9.1, 5.3)
4	90.3	94.7	-4.4	(-9.3, 0.3)
5	82.0	76.9	5.1	(-2.2, 12.4)
6A	93.2	94.8	-1.6	(-6.1, 2.6)
6B	94.2	94.0	0.3	(-4.0, 4.6)
7F	82.5	86.3	-3.8	(-10.3, 2.7)
9V	80.2	83.5	-3.3	(-10.2, 3.6)
14	94.3	94.1	0.3	(-4.1, 4.7)
18C	94.4	95.5	-1.1	(-5.2, 2.9)
19A	95.2	93.1	2.1	(-2.1, 6.5)
19F	89.5	88.4	1.0	(-4.6, 6.8)
23F	78.6	80.6	-2.0	(-9.2, 5.2)

•Lower 95% CI for the difference between groups was >-10.0 for most serotypes

4.6.2.2 Overall Immunogenicity Conclusions, Study 3008

The predefined non-inferiority criterion (ie, lower limit for the 95% CI for the difference in proportion of responders >-10%) was met after 13vPnC+TIV compared with placebo+TIV in group 1 (13vPnC+TIV/placebo) and group 2 (placebo+TIV/13vPnC), respectively, for A/H1N1 and B, but not for A/H3N2. The difference in proportions of responders to A/H3N2 was -4.6%, with a lower limit of the 95% CI of -10.4%, just below the predefined value for non-inferiority. However, all criteria proposed in the EMA guidance for the annual release of inactivated influenza vaccine were exceeded for all 3 influenza antigens after 13vPnC+TIV in group 1 (13vPnC+TIV/placebo). Notably, the proportions of subjects achieving HAI titers ≥40 were 94.0%, 96.5%, and 81.9% for A/H1N1, A/H3N2, and B strains, respectively, and exceeded the EMA guidance of >60%. Likewise the FDA guideline that the lower bound of the 2-sided 95%

CI of subjects achieving HAI antibody titer ≥40 be ≥60% for adults over 65 years of age was met by the 3 strains.

Comparison of pneumococcal IgG GMCs measured 1 month after 13vPnC+TIV (dose 1) relative to 1 month after 13vPnC alone (dose 2) in group 1 (13vPnC+TIV/placebo) and in group 2 (placebo+TIV/13vPnC), respectively, showed that the predefined non-inferiority criterion (ie, the lower limit of the 2-sided 95% CI for the ratio of >0.5) was met for all serotypes except for 19F; the lower limit of the 95% CI for the ratio for 19F was 0.49. However, IgG responses were statistically lower (upper 95% CI of GMT ratio <1) for 6 of 13 serotypes in adults ≥65 years of age after administration of concomitant 13vPnC and TIV compared to 13vPnC alone. In a post-hoc analysis, OPA responses were consistent with IgG responses (primary endpoint). Hence, when 13vPnC was given concomitantly with TIV, the immune responses to at least some 13vPnC serotypes were lower compared to responses when 13vPnC was given alone. The concomitant use of 13vPnC and TIV should be dictated by clinical circumstances.

4.7 Evaluation of 13vPnC in High-Risk Populations and by Gender

4.7.1 High-Risk Populations

When results were adjusted for a history of smoking, the 004 and 3001 trials revealed comparable results as those in the unadjusted population. Each trial included immunocompetent subjects with stable underlying conditions such as chronic cardiovascular disease, chronic pulmonary disease, chronic liver disease, diabetes mellitus, and renal disorders, because it is known that these are common conditions in adults at increased risk of serious pneumococcal CAP and IPD. Subjects with preexisting stable disease (defined as disease not requiring significant change in therapy or hospitalization for worsening disease 12 weeks before receipt of study vaccine) were eligible.

When examining serial responses after 1 or 2 doses in both 23vPS-naïve and preimmunized subjects, patterns of response were comparable to the study group from which they were derived. Each high-risk group demonstrated a rise in antibody titer compared to preimmunization titers, after each of 1 or 2 doses was administered. In circumstances in which statistically higher responses were observed after 13vPnC by GMFRs or comparisons of GMTs, point estimates

trended higher in these subgroups. The findings indicate that these high-risk adults are likely to receive analogous benefits to those in healthier older adults.

4.7.2 Gender

Because gender distribution in study 004 was statistically significantly different in the 2 vaccine groups in cohort 1 (p=0.0285), in which more female than male subjects were enrolled, an ad hoc analysis of serotype-specific OPA titers and proportion of subjects achieving an OPA titer ≥LLOQ for each serotype 1 month after vaccination was performed for each gender.

A gender analysis was also run in study 3005 in 23vPS-preimmunized subjects. The analyses revealed no apparent impact on overall conclusions for either study.

4.8 Overall Conclusions Regarding the Use of 13vPnC Based on Immunogenicity Results

The following overall conclusions regarding use of 13vPnC are supported by the observations in the reported studies.

Irrespective of age or 23vPS immunization status, initial and subsequent immunization for prevention of pneumococcal disease should be preferably administered using the 13vPnC conjugate vaccine. In contrast to 23vPS, 13vPnC elicits an enhanced functional anti-pneumococcal immune response to the 12 serotypes in common to both vaccines, as well as a strongly enhanced response to serotype 6A (which likely also provides a cross-reactive response to 6C).[150] 13vPnC induces statistically higher antibody responses than 23vPS in both pneumococcal vaccine-naïve and 23vPS-experienced adults. In addition, 13vPnC elicits a memory response and, accordingly, permits revaccination that maintains or improves antibody levels after a 1-year interval in 23vPS-preimmunized adults, and after 3.5 to 4 years in vaccine-naïve adults. By contrast, administration of 23vPS vaccine is associated with absence of immunologic memory, and has a negative impact on immunologic response to subsequent 13vPnC or 23vPS administration.

When 13vPnC is administered with TIV, responses to TIV are comparable to responses after TIV alone. Functional serotype-specific OPA antibody responses are diminished when 13vPnC

is administered with TIV, and therefore concomitant use of these vaccines should be dictated by clinical circumstances.

Given its immunologic advantages, 13vPnC has the potential to provide a greater degree of protection against pneumococcal disease, including pneumococcal CAP, in both 23vPS-preimmunized and 23vPS-naïve individuals, compared to administration of the 23vPS vaccine. The ability to establish memory and, hence, maintain the anti-pneumococcal immune response through revaccination supports the perspective that immunization with 13vPnC should occur as early as 50 years of age, given the general increase in pneumococcal disease observed after this age and the reduction in vaccine response that occurs with advancing age. Immunocompetent adults with underlying risk conditions that place them at increased risk of pneumococcal disease are also likely to benefit from this strategy.

13vPnC will address the unmet medical need of providing greater protection against pneumococcal disease including community-acquired pneumonia over a longer age range. The ongoing CAPiTA study is designed to confirm the ability of 13vPnC to elicit protection against vaccine serotype-specific community-acquired pneumonia, as a post-licensure commitment. Additional work is also underway (see Section 8.0) to further evaluate the interval for reimmunization with 13vPnC to best maintain functional OPA responses.

5.0 OVERVIEW OF SAFETY

Over 6000 adults ≥50 years of age received 13vPnC in trials supporting the use of this vaccine. Safety data obtained from more than 5,600 adults who received at least 1 dose of 13vPnC in the 6 phase 3 trials are summarized in this overview. The same 13vPnC formulation licensed and marketed for infants was used in all 6 of these phase 3 adult studies included in the summary of safety data. The 6 studies (004, 3010, 3001, 3008, 3000, 3005) were conducted in various countries in Europe and the United States. In addition, data from the clinical study report for the 004 extension study, submitted to the FDA on August 31, 2011, are also provided for those subjects who received both a first and second dose of pneumococcal vaccine.

5.1 Safety Database

The number of naïve and preimmunized subjects receiving at least 1 dose of 13vPnC in each study are provided in Table 5-1. The total number of subjects receiving 13vPnC by age group is presented in Table 5-2.

Table 5-1: Number of Subjects Receiving 13vPnC to Support Indication for Use in Adults ≥50 yo

Study	Brief Description	Naive	23vPS Pre-immunized
004	Pivotal non-inferiority study vs 23vPS in 23vPS naives (50-59 & 60-64)	821	
3010	Sequential vaccination (60-64y yo naive)	701	
3008	Concomitant TIV (≥65 yo naive)	1135	
3001	Concomitant TIV (50-59y yo naive)	1094	
3000	Safety study in 23vPS pre-immunized (≥68 yo)		1049
3005	Pivotal non-inferiority study vs 23vPS in 23vPS pre-immunized (≥70 yo)		867
	Total number of subjects in each category	3751	1916
	TOTAL number subjects with 13vPnC	5667	

Table 5-2: Number (%) of Subjects Receiving 13vPnC by Age Group

Age (years)	Number (%)
50-64 yo	2616 (46.2)
65-69 yo	646 (11.4)
70-74 yo	1139 (20.1)
75-79 yo	760 (13.4)
≥80 yo	506 (8.9)
Total	5667 (100.0)

Safety assessments of initial and subsequent study doses of pneumococcal vaccine administered 1 year apart were evaluated in 2 studies (3010 and 3005). A total 1445 subjects received vaccination 2 in a sequence of 2 pneumococcal vaccines in these studies; 650 subjects were naïve and 795 preimmunized.

A total of 16 subjects were withdrawn from the studies because of adverse events (AEs). Among the subjects withdrawn because of AEs, 5 had received 13vPnC, 9 had received 23vPS, 1 had received TIV+placebo, and 1 had received placebo only. The most frequent AE type resulting in withdrawal from study was cancer. Sixteen (16) subjects died; all deaths were considered not vaccine-related.

5.2 Population

Across all adult studies, subjects ranged in age from 50 years to ≥70 years at the time of the first dose of 13vPnC; the oldest subject was 93 years of age. In the 4 studies in 23vPS-naïve subjects, previous vaccination with a registered or an investigational pneumococcal vaccine was an exclusion criterion. In the 2 studies in 23vPS-preimmunized subjects, previous 23vPS doses had to be documented by the study subjects.

A written and dated informed consent was obtained from all study subjects.

5.3 Limitations of the Safety Database

The study population encompassing all trials represented adults ≥50 years of age. Subjects with underlying chronic medical conditions not compromising the immune system were allowed to be enrolled, provided that the underlying disease was stable. Stable disease was defined as disease not requiring significant change in therapy[a] or hospitalization for worsening disease for 12 weeks before receipt of study vaccine.

The safety of 13vPnC is currently being evaluated in immunocompromised high-risk subjects, but is not part of this submission. Such studies are currently in progress for children and adults with HIV infection, children and adults after hematopoietic stem cell transplant, and children and adults with sickle cell disease.

The size of the safety database may be too small to detect rare AEs that would occur at a frequency lower than 0.1%. Therefore, the applicant plans to provide safety data from the 84,496 subjects in the ongoing efficacy study (6115A1-3006; Community-Acquired Pneumonia Immunization Trial in Adults [CAPITA]) as a postmarketing commitment.

5.4 Summary of Key Safety Results

5.4.1 Analysis of Adverse Reactions

The safety of 13vPnC was evaluated on the basis of prompted AEs, including local reactions and systemic events, as well as spontaneously reported AEs. Data on prompted AEs were recorded daily by the study subjects for 14 days after each dose. Because of the diversity of study designs and the different ages of the populations evaluated, no integration or meta-analyses of safety data were performed. Therefore, the overview of safety is based on individual study data and, where appropriate, comparison of data across studies.

[a] Change in dose or therapy within a category (eg, change from 1 nonsteroidal anti-inflammatory drug [NSAID] to another) was allowed. Change to new therapy categories (eg, surgery or addition of a new pharmacologic class) was allowed only if it was not caused by worsening disease. A change to new therapy categories caused by worsening disease was considered significant.

5.4.2 Prompted Adverse Events

5.4.2.1 Local Reactions

Comparisons of local reactions after the first study dose of either 13vPnC or 23vPS are summarized in Figure 5-1 to Figure 5-4.

5.4.2.1.1 13vPnC in 23vPS-Naïve Subjects Across Studies

The incidence of redness reported after an initial study vaccination of 13vPnC was similar across all studies including 23vPS-naïve subjects, ranging between 10.8% and 20.2%, with no apparent differences among the age groups (or between naïve and preimmunized subjects). In each of the studies, most reports were mild, and the incidence of severe redness was ≤1.7%. Similar results were observed for swelling at the injection site: across studies, the incidence of swelling ranged between 10.0% and 21.7%; most reports were mild, and in each study severe swelling was reported by ≤0.6% of subjects receiving an initial vaccination of 13vPnC.

Pain at the injection site was more frequent in younger than in older subjects, ranging from 69.2% to 88.8% in subjects <65 years old and 41.7% to 51.7 % among subjects ≥65 years of age. The incidence of moderate pain ranged from 20.1% to 40.1% among subjects <65 years of age and from 7.5% to 17.2% among subjects ≥65 years of age. Severe pain was reported most frequently among subjects 50 to 59 years of age (3.6% in study 004, 4.5% in study 3001). Similarly, the incidence of limitation of arm movement was higher in younger subjects: 39.1% to 40.7% in subjects 50 to 59 years of age, 23.5% to 28.5% in subjects 60 to 64 years of age; and 10.5% to 16.2% among subjects ≥65 years of age. Limitation of arm movement was most frequently reported as mild, and was reported as severe in ≤2.9% of subjects in any study.

5.4.2.1.2 Comparison of Local Reactions After 13vPnC in 23vPS-Naïve and 23vPS-Preimmunized Subjects

The incidence for most local reactions after 13vPnC was similar between 23vPS-naïve and 23vPS-preimmunized subjects of similar age groups (≥68 years in studies 3000 and 3005, preimmunized, and ≥65 years in study 3008, naïve), except for pain which was reported somewhat more often in prevaccinated subjects (51.0% to 51.7%) than in 23vPS-naïve subjects (41.7%). Although subjects have similar age in these studies, age-related differences between studies cannot be excluded. The incidence of pain in elderly preimmunized subjects (≥68 years)

was substantially below that in naïve younger subjects (50 to 64 years); however, this numerical difference is not considered clinically meaningful.

Although study 3000 allowed 1 or more prior doses of 23vPS, all subjects enrolled had only a single prior dose of 23vPS. The incidences of local reactions observed are similar compared to study 3005, for which a single prior dose of 23vPS was a requirement.

Overall, these results suggest that vaccination with 23vPS three to more than five years before vaccination with 13vPnC did not affect local reactogenicity after vaccination with 13vPnC.

5.4.2.1.3 Local Reactions: 13vPnC Compared to 23vPS in 23vPS-Naïve Subjects

In subjects 60 to 64 years of age and naïve to 23vPS, redness, swelling, and limitation of arm movement were reported at similar incidence after vaccination with 13vPnC or 23vPS (studies 004, 3010). Pain was reported in both studies more frequently after vaccination with 13vPnC (80.1% and 69.2%) compared to vaccination with 23vPS (73.4% and 58.3%, Figure 5-1 to Figure 5-4).

5.4.2.1.4 Local Reactions: 13vPnC Compared to 23vPS in 23vPS-Preimmunized Subjects

In subjects ≥70 years of age who had previously received one dose of 23vPS at least 5 years before vaccination with 13vPnC or 23vPS, the incidence of local reactions was lower for all 4 reaction types and for all gradings in subjects who received 13vPnC compared to subjects who received 23vPS (Figure 5-1 to Figure 5-4).

The incidences reported for redness, swelling, and limitation of arm movement after 13vPnC ranged from 10.4% to 10.8%, and after 23vPS from 22.2% to 27.6%. Pain was the most frequently observed local reaction after 13vPnC (51.7%) and after 23vPS (58.5%) and was mostly mild (50.1% and 54.1%, respectively). Moderate and severe pain was reported more frequently after 23vPS (23.6% and 2.3%) compared to 13vPnC (7.5% and 1.3%), respectively.

Severe redness, swelling, and limitation of arm movement were statistically significantly higher in 23vPS recipients compared to 13vPnC recipients (study 3005).

These results indicate that subjects preimmunized with 23vPS five or more years earlier, have significantly higher local reactogenicity when revaccinated with another dose of 23vPS, compared to vaccination with 13vPnC.

Figure 5-1: Studies 004, 3010, 3005 – Subjects Reporting Local Reaction at Year 0 - Redness

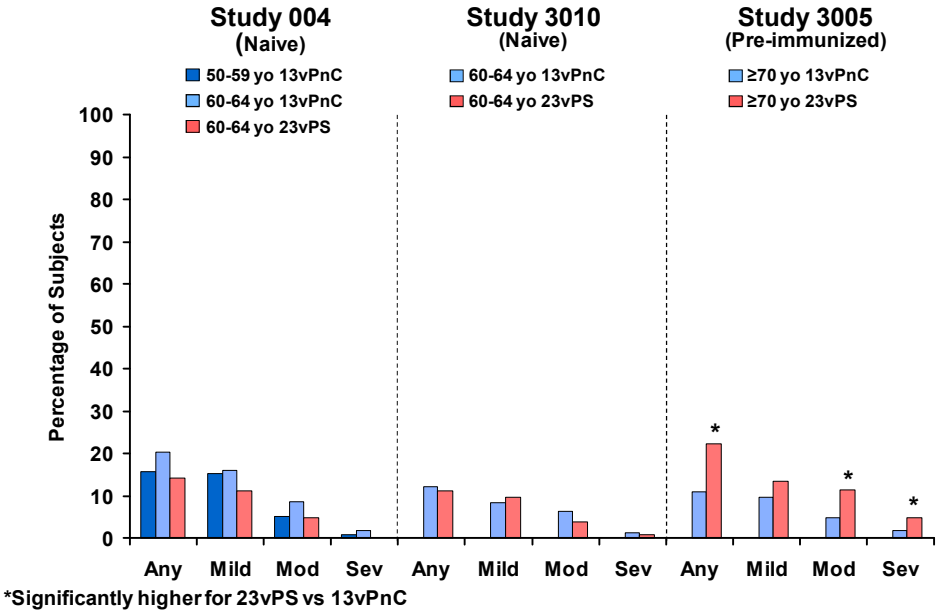


Figure 5-2: Studies 004, 3010, 3005 – Subjects Reporting Local Reaction at Year 0 - Swelling

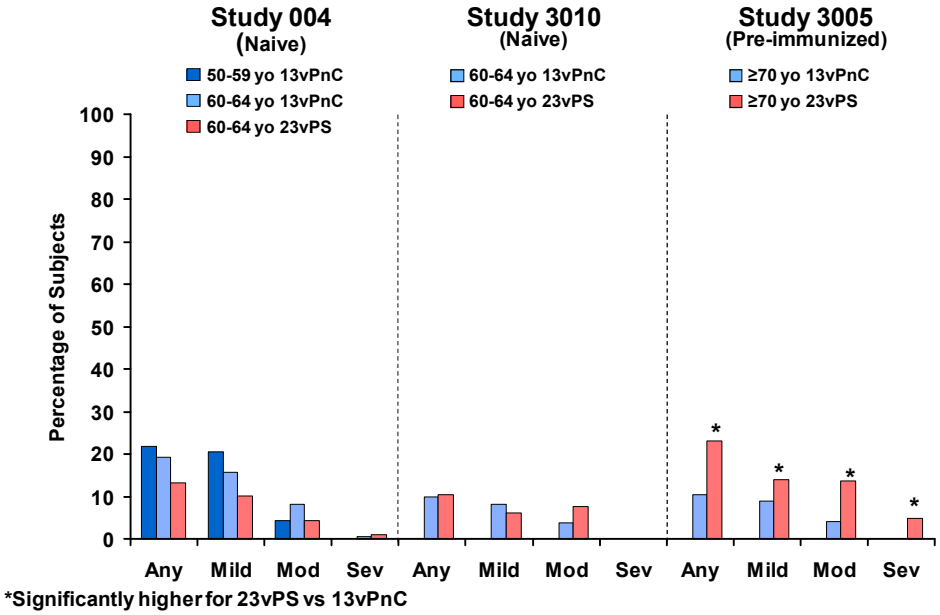


Figure 5-3: Studies 004, 3010, 3005 – Subjects Reporting Local Reaction at Year 0 - Pain

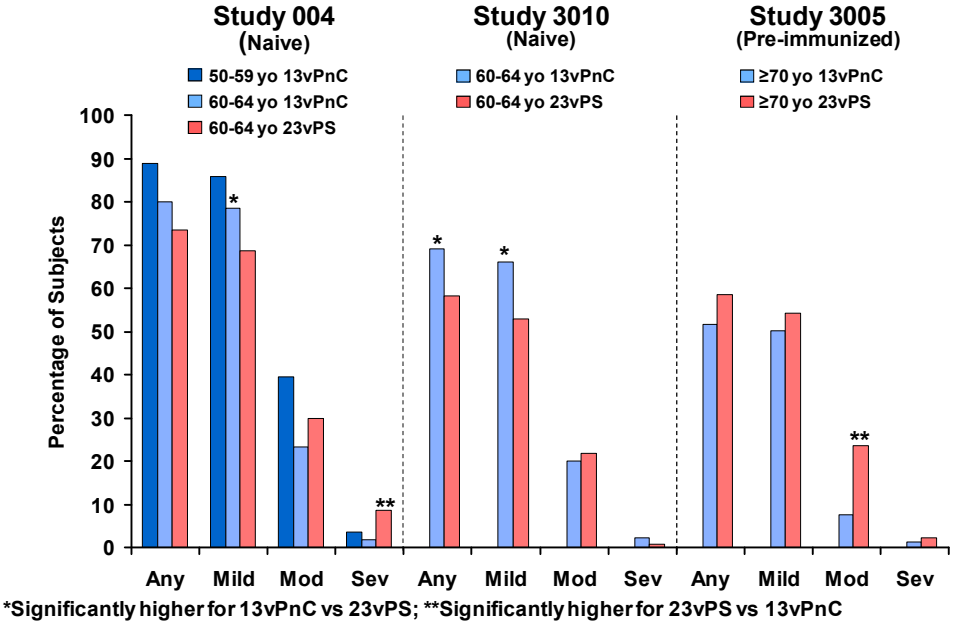
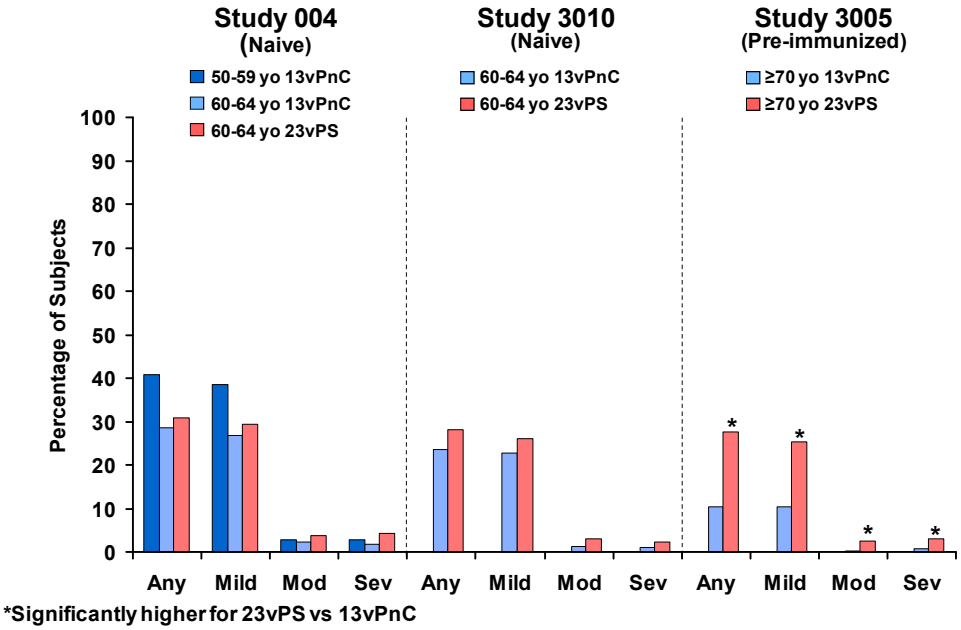


Figure 5-4: Studies 004, 3010, 3005 – Subjects Reporting Local Reaction at Year 0 – Limitation of Arm Movement



5.4.2.1.5 Local Reactions: 13vPnC and 23vPS Administered in 2-Vaccine Sequences in 23vPS-Naïve Subjects, Study 3010

Local reactions were assessed in subjects 60 to 64 years of age naïve to 23vPS in study 3010. Subjects received either an initial dose of 13vPnC or 23vPS. 13vPnC recipients were vaccinated 1 year later with either 13vPnC or 23vPS. 23vPS recipients were vaccinated 1 year later with 13vPnC.

13vPnC vs 13vPnC/13vPnC: All 4 local reaction types were reported at similar frequency (Figure 5-5). Pain and limitation of arm movement were the 2 reaction types most frequently observed. After 13vPnC and 13vPnC/13vPnC, pain was reported by 76.9% and 75.9% of subjects, and limitation of arm movement was reported by 26.2% and 24.6% of subjects, respectively. Redness and swelling ranged between 10.0% and 14.8%. The incidence of severe reports after each vaccination was ≤3.5%.

13vPnC vs 23vPS/13vPnC: Local reaction types were reported at similar frequency after 13vPnC and 23vPS/13vPnC except redness, which was 12.2% after 13vPnC compared to 4.3% after 23vPS/13vPnC (Figure 5-6). Pain and limitation of arm movement were the 2 reaction types most frequently observed. After 13vPnC and 23vPS/13vPnC, pain was reported by 69.2% and 69.8% of subjects, and limitation of arm movement was reported by 23.5% and 18.5% of subjects, respectively. Redness and swelling ranged between 4.3% and 12.2%. The incidence of severe reports after each vaccination was ≤2.3%.

23vPS vs 13vPnC/23vPS: All 4 reaction types were statistically significantly higher after 13vPnC/23vPS compared to 23vPS alone, with the exception of moderate swelling (Figure 5-7). Pain and limitation of arm movement were the 2 reaction types most frequently observed. After 23vPS and 13vPnC/23vPS, pain was reported by 58.3% compared to 85.7% of subjects, and limitation of arm movement was reported by 28.2% compared to 53.4% of subjects, respectively.

Likewise, after 23vPS and 13vPnC/23vPS, redness was reported by 11.2% compared to 27.8% of subjects, and swelling was reported by 10.4% compared to 25.8%, respectively. The highest incidence of severe reports was 12.9% for severe pain after 13vPnC/23vPS.

13vPnC/13vPnC, 13vPnC/23vPS, and 23vPS/13vPnC comparisons: Pain at the injection site was reported most frequently, followed by limitation of arm movement, swelling, and redness (Figure 5-8 to Figure 5-11). The incidences for all types of local reactions were highest for the sequence 13vPnC/23vPS, followed by 13vPnC/13vPnC, and lowest for 23vPS/13vPnC. Pain, the most frequently reported local reaction was lowest (69.8%) after 23vPS/13vPnC, and highest after 13vPnC/23vPS (85.7%). Limitation of arm movement was lowest after 23vPS/13vPnC (18.5%) and highest after 13vPnC/23vPS (53.4%).

The lowest incidences for redness and swelling after 23vPS/13vPnC were 4.3% and 5%, respectively; the highest incidences after 13vPnC/23vPS were 27.8% for redness and 25.8% for swelling.

For all local reactions, the incidences after 13vPnC/13vPnC were lower than after 13vPnC/23vPS, but higher than after 23vPS/13vPnC. Severe reactions were most frequently reported after 13vPnC/23vPS with 12.9% for pain and 8.1% for limitation of arm movement.

Figure 5-5: Study 3010 – Naïve Subjects 60-64 yo Reporting Local Reactions 13vPnC vs 13vPnC/13vPnC

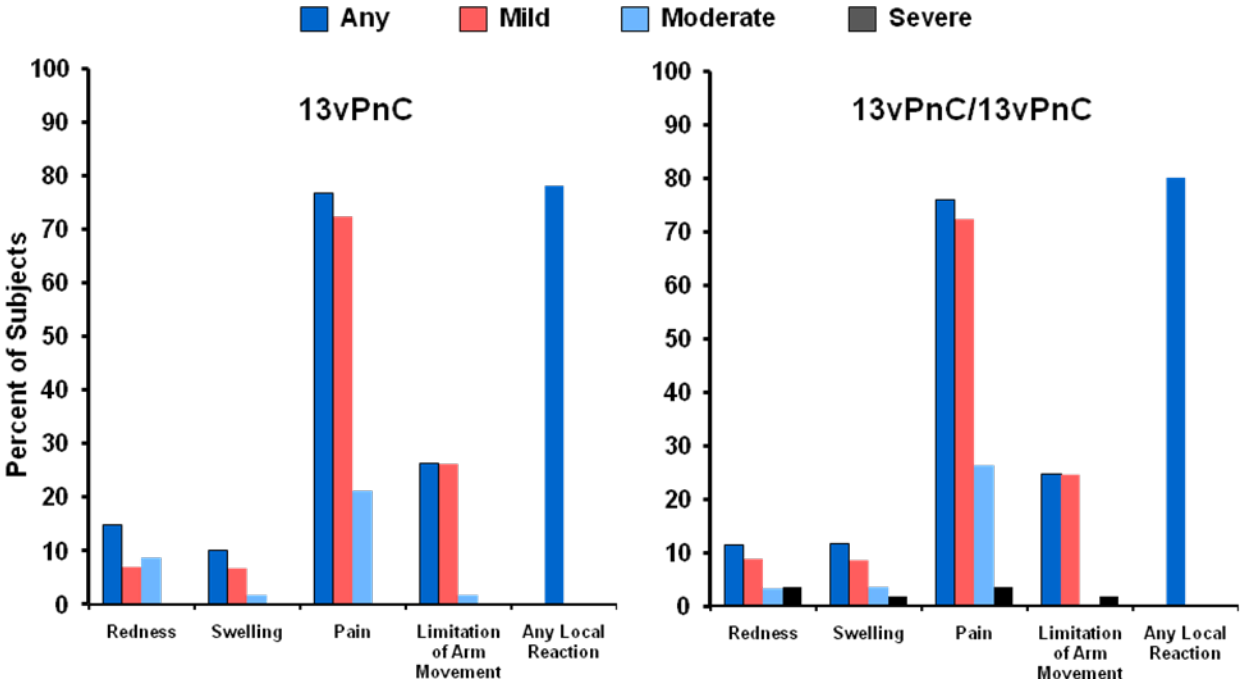


Figure 5-6: Study 3010 – Naïve Subjects 60-64 yo Reporting Local Reactions 13vPnC vs 23vPS/13vPnC

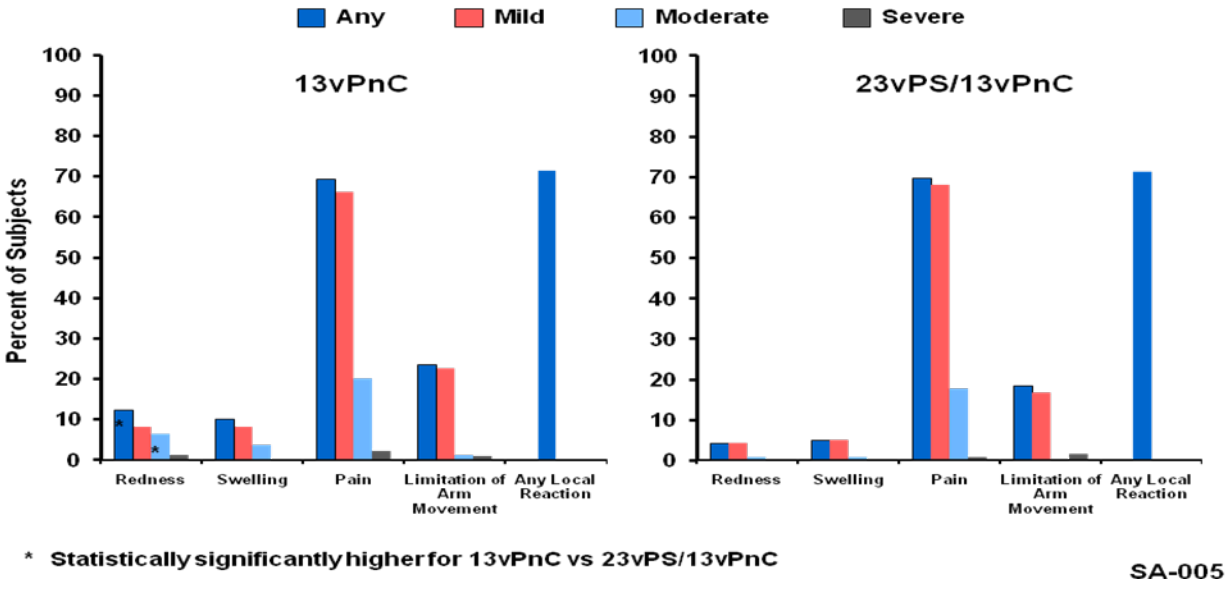


Figure 5-7: Study 3010 – Naïve Subjects 60-64 yo Reporting Local Reactions 23vPS vs 13vPnC/23vPS

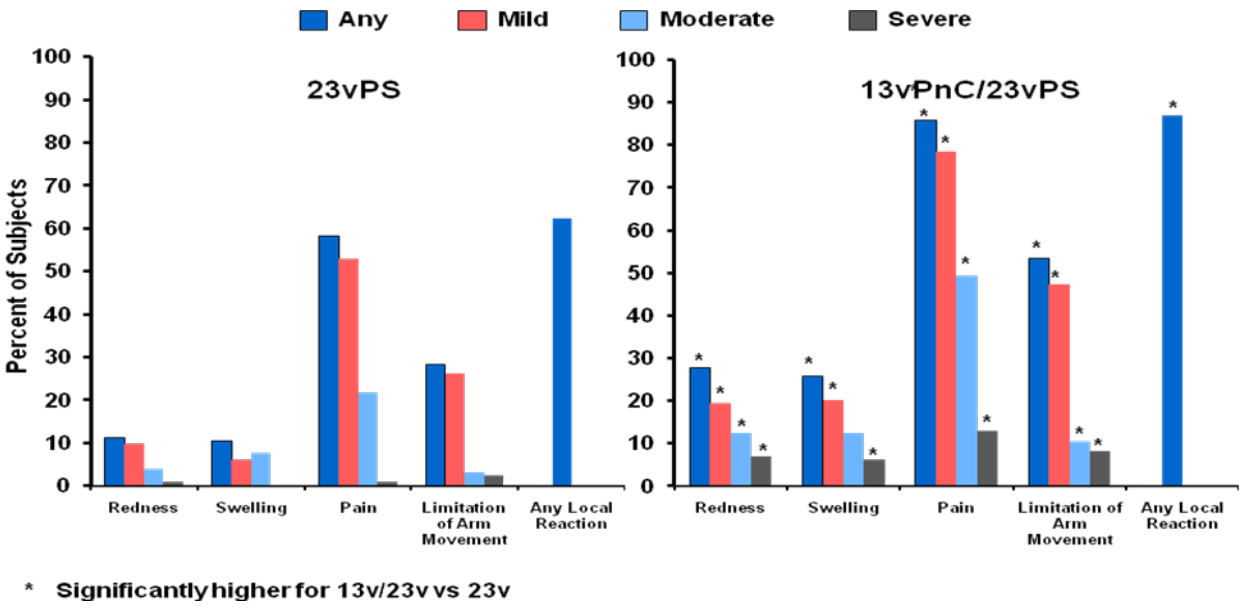
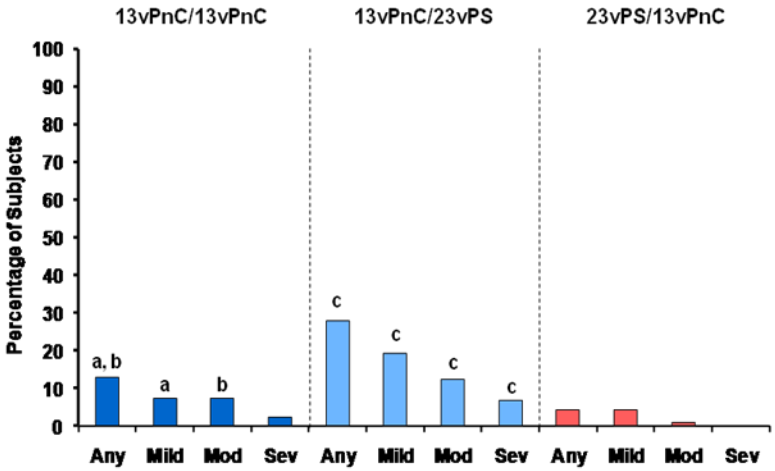
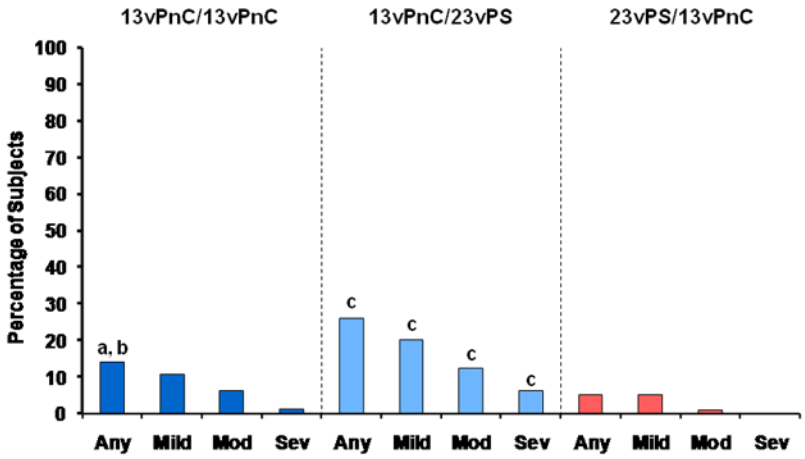


Figure 5-8: Study 3010 – Naïve Subjects 60-64 yo Reporting Redness After Vaccination 2 (Year 1)



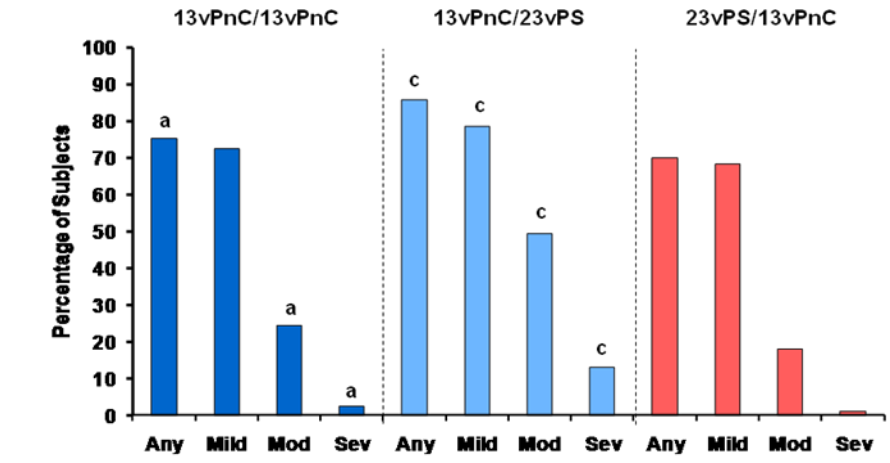
Significantly different for:
a: 13vPnC/13vPnC vs 13vPnC/23vPS
b: 13vPnC/13vPnC vs 23vPS/13vPnC
c: 13vPnC/23vPS vs 23vPS/13vPnC

Figure 5-9: Study 3010 – Naïve Subjects 60-64 yo Reporting Swelling After Vaccination 2 (Year 1)



Significantly different for:
a: 13vPnC/13vPnC vs 13vPnC/23vPS
b: 13vPnC/13vPnC vs 23vPS/13vPnC
c: 13vPnC/23vPS vs 23vPS/13vPnC

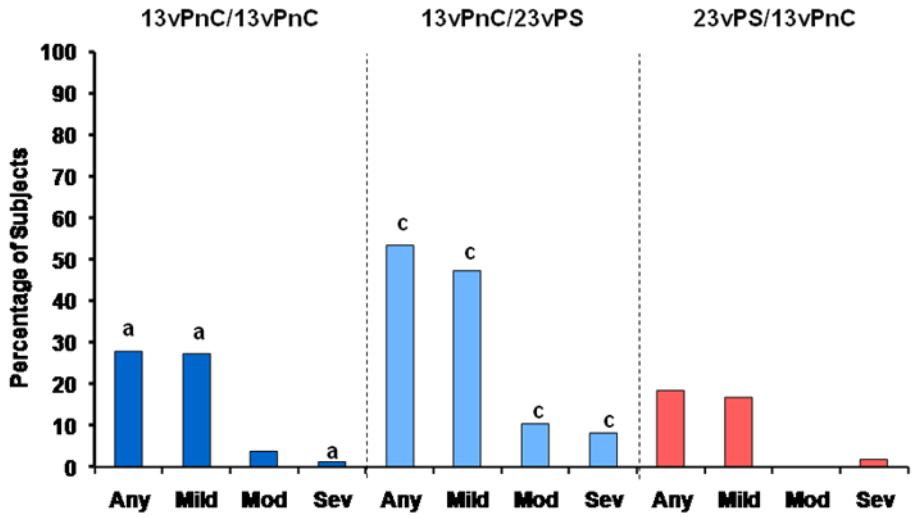
Figure 5-10: Study 3010 – Naïve Subjects 60-64 yo Reporting Pain After Vaccination 2 (Year 1)



Significantly different for:
a: 13vPnC/13vPnC vs 13vPnC/23vPS
b: 13vPnC/13vPnC vs 23vPS/13vPnC
c: 13vPnC/23vPS vs 23vPS/13vPnC

SA-011

Figure 5-11: Study 3010 – Naïve Subjects 60-64 yo Reporting Limitation of Arm Movement After Vaccination 2 (Year 1)



Significantly different for:
a: 13vPnC/13vPnC vs 13vPnC/23vPS
b: 13vPnC/13vPnC vs 23vPS/13vPnC
c: 13vPnC/23vPS vs 23vPS/13vPnC

5.4.2.1.6 Local Reactions: 13vPnC and 23vPS Administered in 2-Vaccine Sequences in 23vPS-Naïve Subjects, Study 004 Extension

Data from the 004 extension study on local reactions after a second dose of vaccine (13vPnC/23vPS, 13vPnC/13vPnC, and 23vPS/23vPS) have recently become available and a clinical study report including these data was provided to the FDA on August 31, 2011. This report provides information on administration of these vaccines with a 3.5 to 4-year interval between doses, for those subjects who received both doses.

Findings after 13vPnC/13vPnC compared to 13vPnC with a 3.5 to 4-year interval between doses recapitulate those seen in 3010 with a 1-year interval. The incidence of local reactions after the second dose was generally comparable or less than that after the first dose in the 60 to 64-year-old cohort and the 50 to 59-year-old cohort (except for a statistically higher incidence of moderate pain in the latter), as shown in Figure 5-12 and Figure 5-13.

Figure 5-12: Study 004 Ext – Naïve Subjects 60-64 yo Reporting Local Reactions 13vPnC vs 13vPnC/13vPnC

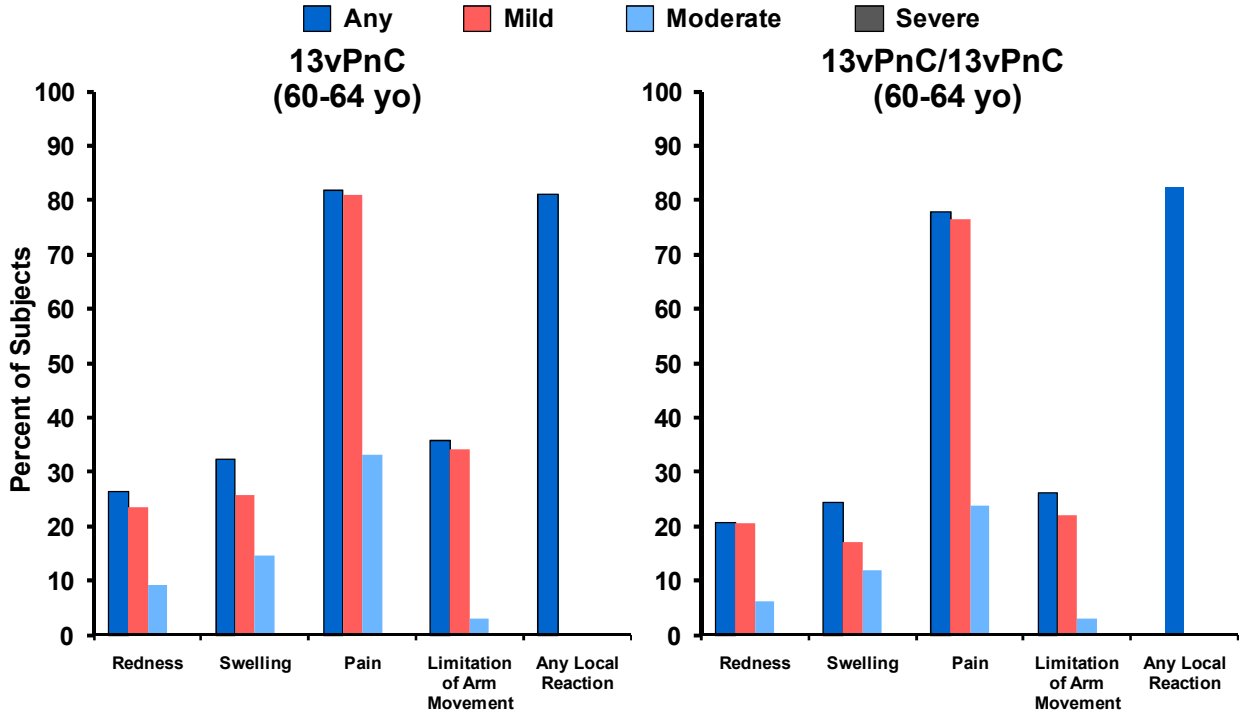
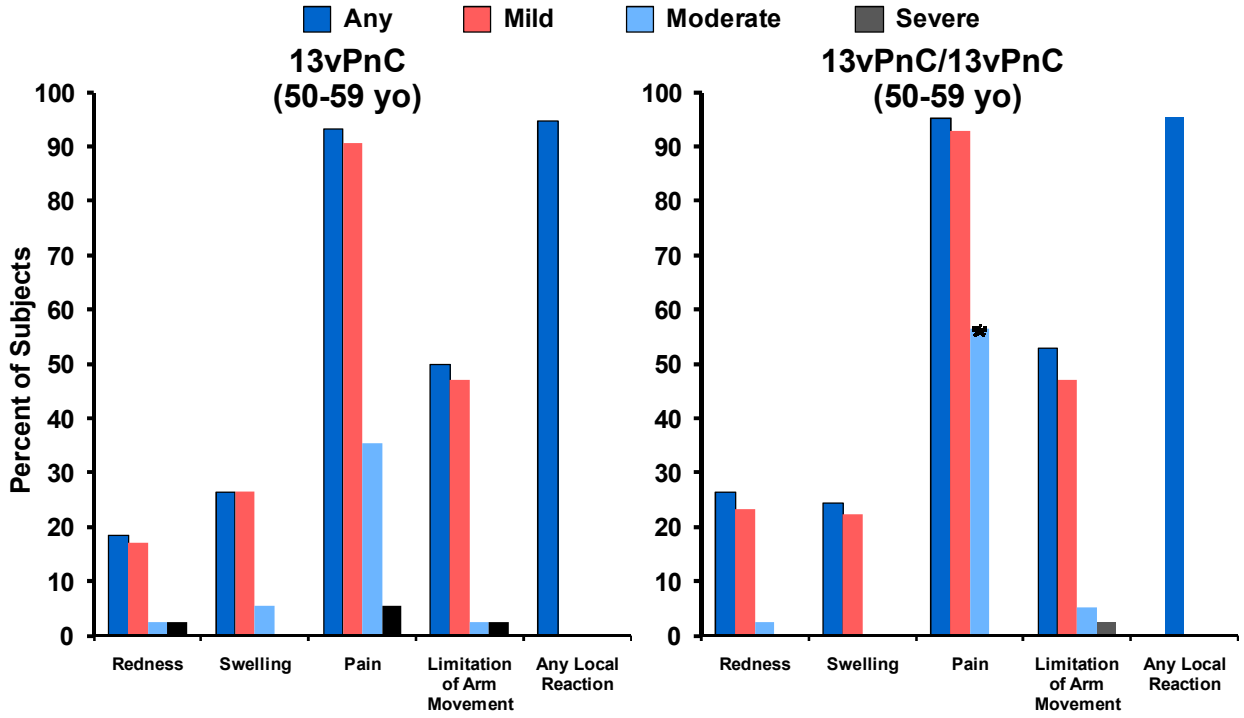


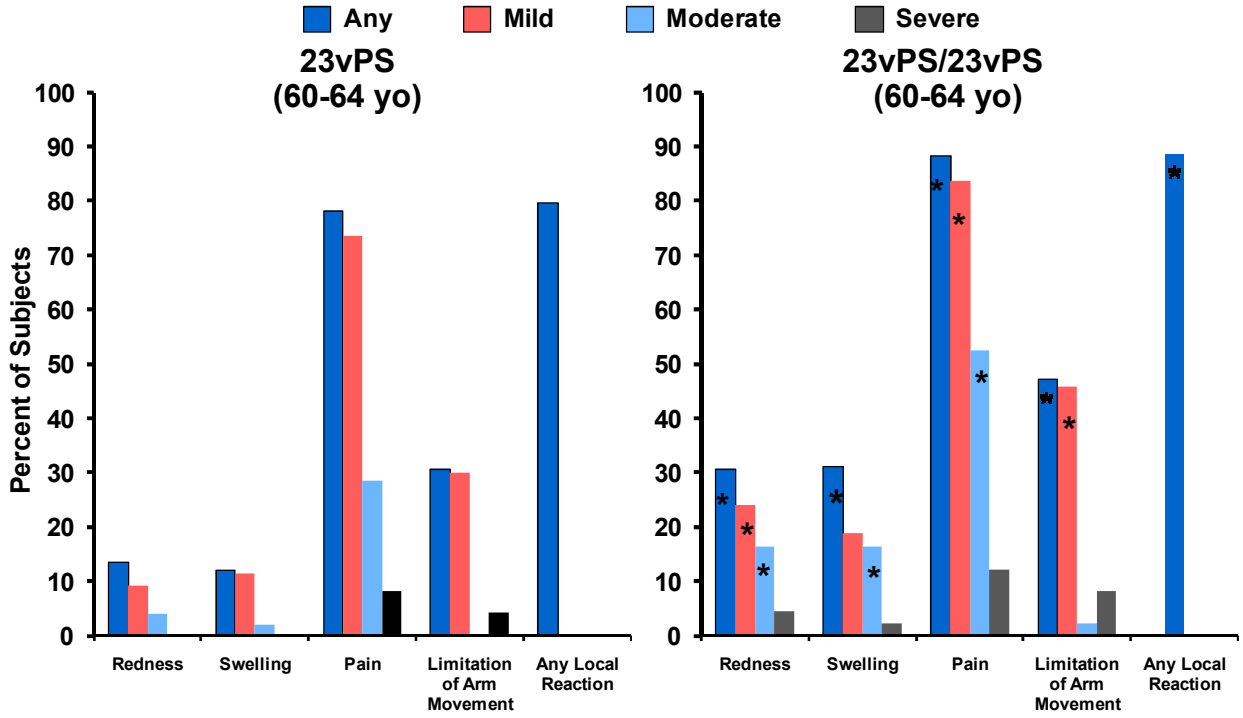
Figure 5-13: Study 004 Ext – Naïve Subjects 50-59 yo Reporting Local Reactions 13vPnC vs 13vPnC/13vPnC



* Statistically significantly higher for 13vPnC/13vPnC vs 13vPnC

The comparable or lower local reactions seen after a second dose of 13vPnC compared to the first dose in the 60 to 64-year-old cohort stands in contrast to nearly uniform higher local reaction rates seen after a second dose of 23vPS compared to a first dose in the sequence 23vPS/23vPS. The incidences of redness, pain, swelling, and limitation of arm movement increased after a second dose of 23vPS, and in many instances statistically so, compared to a first dose (Figure 5-14).

Figure 5-14: Study 004 Ext – Naïve Subjects 60-64 yo Reporting Local Reactions 23vPS vs 23vPS/23vPS



Local reactions after 23vPS in the sequence 13vPnC/23vPS tended to be higher after the 23vPS dose compared to the first 13vPnC dose (Figure 5-15), but none achieved statistical significance, and point estimates of reaction incidence after 13vPnC/23vPS were almost uniformly lower than those after the 23vPS/23vPS sequence, statistically so for moderate swelling (Figure 5-16).

Figure 5-15: Study 004 Ext – Naïve Subjects 60-64 yo Reporting Local Reactions 13vPnC vs 13vPnC/23vPS

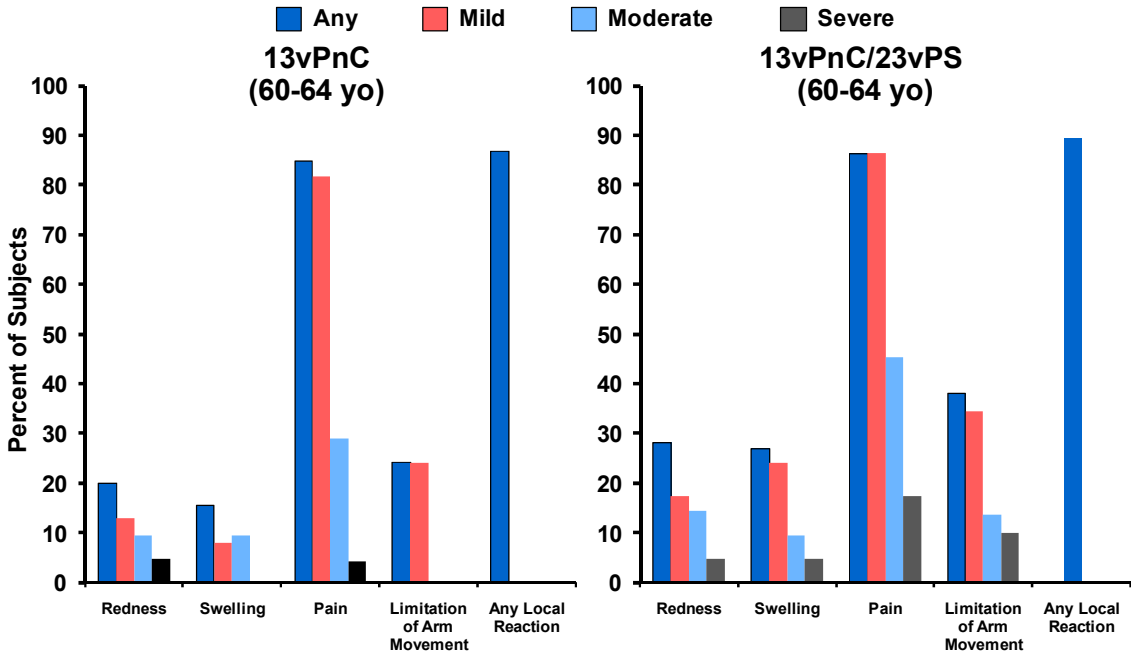
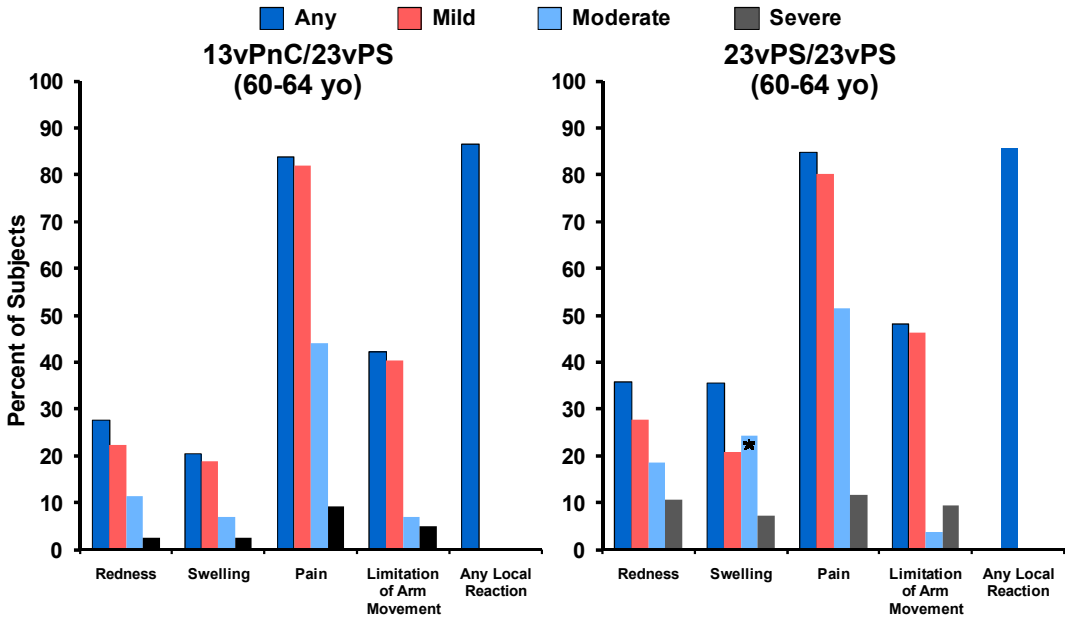


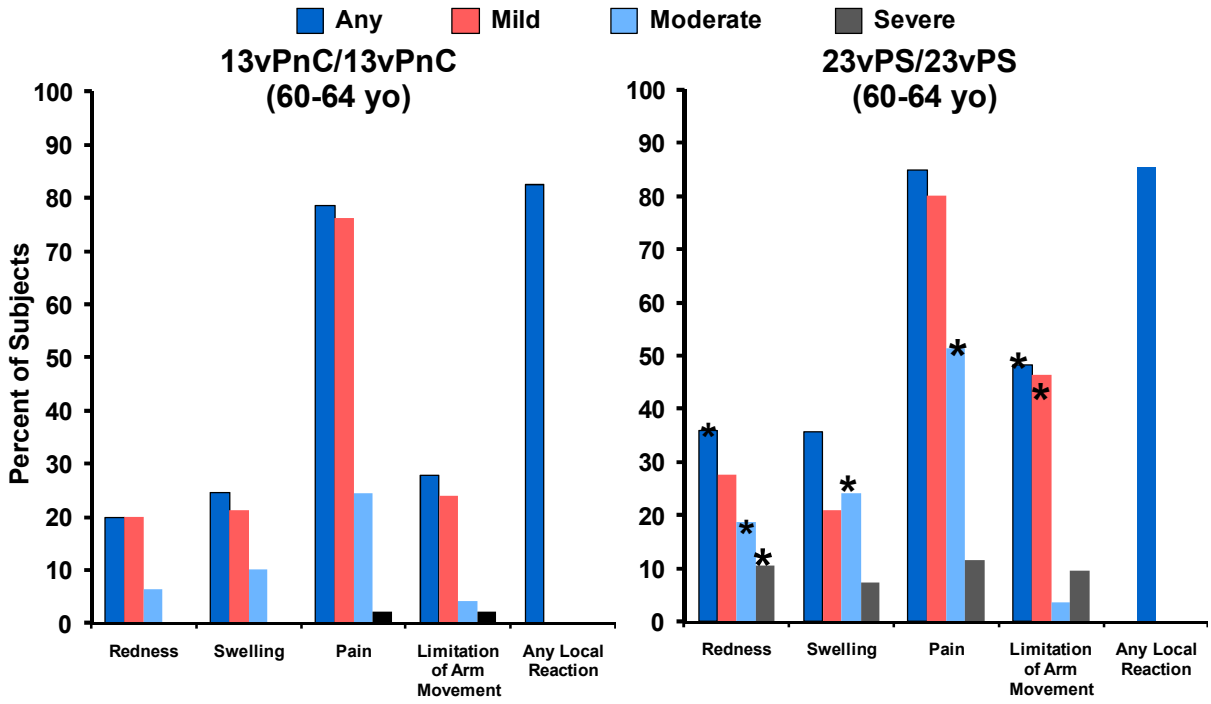
Figure 5-16: Study 004 Ext – Naïve Subjects 60-64 yo Reporting Local Reactions 13vPnC/23vPS vs 23vPS/23vPS



* Statistically significantly higher for 23vPS/23vPS vs 13vPnC/23vPS

Importantly, observed local reactions after 13vPnC/13vPnC were uniformly less common, and in many instances statistically so, compared to reactions after 23vPS/23vPS (Figure 5-17). This provides additional reassurance, that in addition to the immunologic advantages of 13vPnC/13vPnC compared to 23vPS/23vPS (Section 4.5.5.2, Table 4-22), administration of the sequence 13vPnC/13vPnC has a favorable local reactogenicity profile compared to administration of 23vPS/23vPS, when vaccines are administered 3.5 to 4 years apart.

Figure 5-17: Study 004 Ext – Naïve Subjects 60-64 yo Reporting Local Reactions 13vPnC/13vPnC vs 23vPS/23vPS



* Statistically significantly higher for 23vPS/23vPS vs 13vPnC/13vPnC

5.4.2.1.7 Local Reactions: 13vPnC and 23vPS Administered in 2-Vaccine Sequences in 23vPS-Preimmunized Subjects, Study 3005

Local reactions were compared after the sequential study doses of either 13vPnC/13vPnC or 23vPS/13vPnC in preimmunized subjects in study 3005.

Local reactions were assessed in subjects ≥70 years of age preimmunized with 1 dose of 23vPS, five years or more prior to receiving either 13vPnC or 23vPS. All subjects received 1 dose of 13vPnC one year later.

13vPnC vs 13vPnC/13vPnC: All 4 local reaction types were reported at similar frequency after 1 dose of 13vPnC and 2 doses of 13vPnC (Figure 5-18). Pain was the most frequently reported local reaction after 13vPnC alone (55%) or 13vPnC/13vPnC (57.4%.). Redness, swelling, and

limitation of arm movement ranged between 9.2% and 13.3%. The incidence of severe reports after each vaccination was ≤1.7%.

13vPnC vs 23vPS/13vPnC: All reaction types were reported at similar frequency after 1 dose of 13vPnC and after 23vPS/13vPnC except limitation of arm movement which was statistically significantly higher after 23vPS/13vPnC (19.9%) compared to 13vPnC alone (10.5%, Figure 5-19). Local reactions by severity categories were also similar except for statistically significantly higher values after 23vPS/13vPnC than after 13vPnC for moderate pain (13.1% vs 7.5%, respectively) and mild limitation of arm movement (18.9% vs 10.3%, respectively). Pain was the most frequently reported local reaction with 51.7% after 13vPnC alone and 56.6% after 23vPS/13vPnC. Redness and swelling ranged from 10.1% to 14.1%. The incidence of severe reports after each vaccination was ≤1.7%.

13vPnC/13vPnC vs 23vPS/13vPnC: All reaction types were reported at similar frequency after both sequences (Figure 5-20). Pain was the most frequently reported local reaction with 58.2% after 13vPnC/13vPnC and 56.6% after 23vPS/13vPnC. Redness, swelling, and limitation of arm movement ranged between 10.1% and 19.9%. The incidence of severe reports after each vaccination was ≤1.8%.

Figure 5-18: Study 3005 – Preimmunized Subjects ≥70 yo Reporting Local Reactions 13vPnC vs 13vPnC/13vPnC

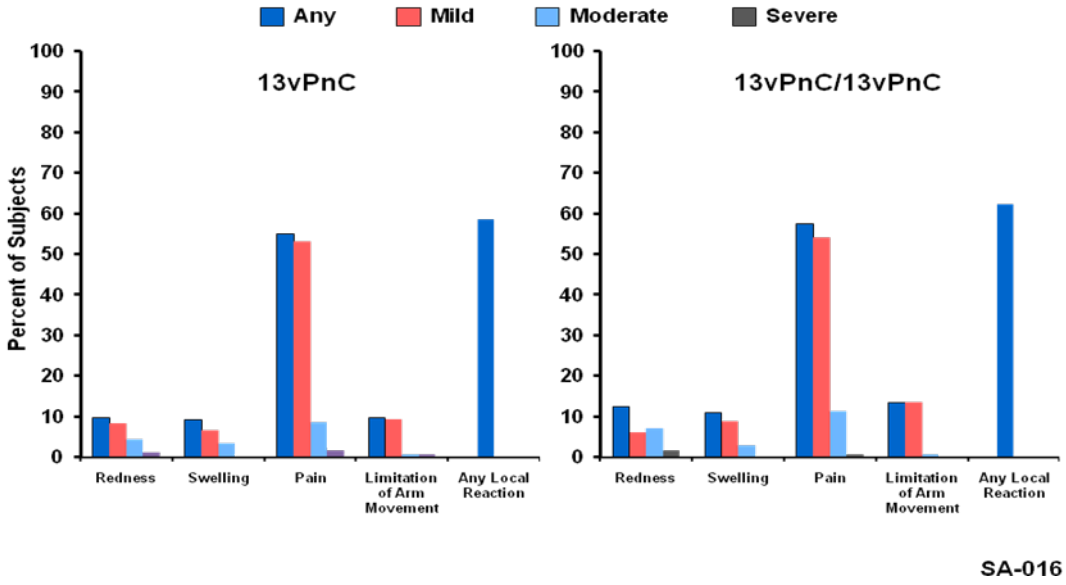


Figure 5-19: Study 3005 – Preimmunized Subjects ≥70 yo Reporting Local Reactions 13vPnC vs 23vPS/13vPnC

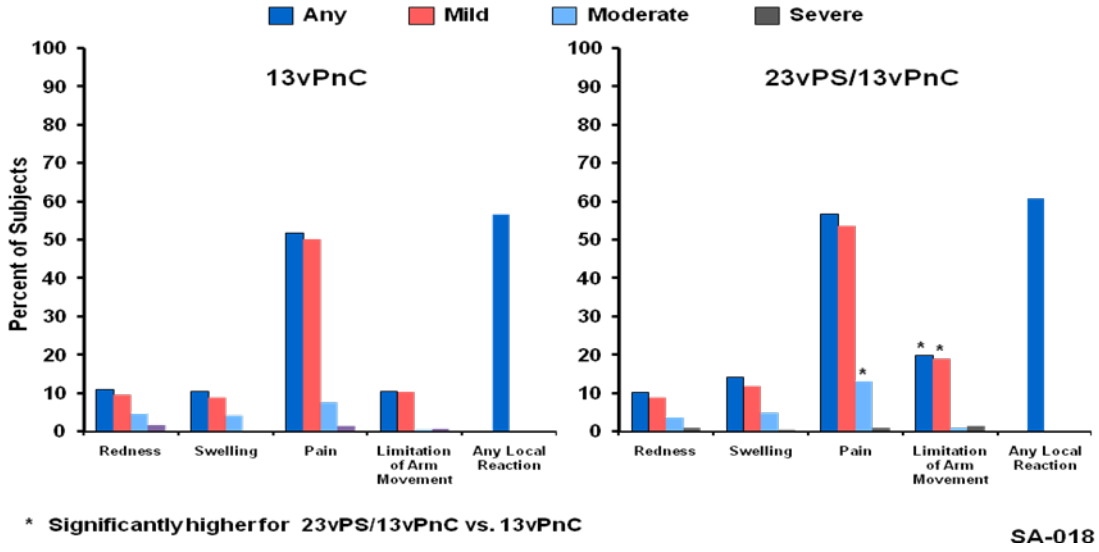
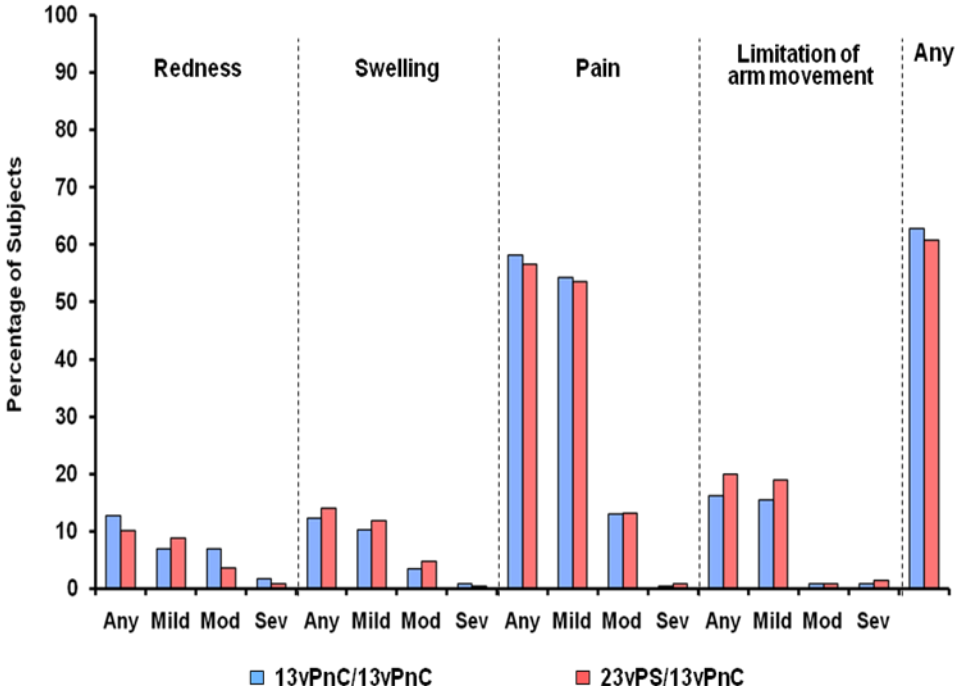


Figure 5-20: Study 3005 – Preimmunized Subjects ≥70 yo Reporting Local Reactions 13vPnC/13vPnC vs 23vPS/13vPnC After Vaccination 2 (Year 1)



5.4.2.1.8 Local Reactions: 13vPnC with Concomitant Administration of Trivalent Influenza Vaccine (TIV)

After concomitant administration of 13vPnC+TIV in subjects 50 to 59 years of age, similar frequencies for all local reactions were observed compared to 13vPnC administered alone. The 2 types of local reaction reported most frequently were pain with 86.8% and 84.5%, and limitation of arm movement with 35.6% and 42.5% after 13vPnC+TIV and 13vPnC alone. Redness and swelling ranged between 12.1% and 18.4%. The incidence of severe reports after each vaccination was ≤4.8%.

After concomitant administration of 13vPnC+TIV in subjects ≥65 year of age, similar frequencies for all local reactions were observed compared to 13vPnC administered alone. The local reaction most frequently reported was pain with 40% and 43.4% after 13vPnC+TIV and

13vPnC alone, respectively. Redness, swelling, and limitation of arm movement ranged between 10.2% and 16.6%.

The incidence of severe reports after each vaccination was ≤2.6%.

Generally, incidences for redness and swelling were similar in the age group 50 to 59 years and ≥65 years. However, pain and limitation of arm movement were reported more frequently in the younger age group compared to the older age group. The incidence of pain was 86.8% and 84.5% in the age group 50 to 59 and 40% and 43.4% in the age group ≥65 years after 13vPnC+TIV and 13vPnC alone, respectively. Limitation of arm movement was reported in 35.6% and 42.5% in the younger age group, and 13.9% and 14.8% in the older age group after 13vPnC+TIV and 13vPnC alone, respectively.

The incidence of severe pain was ≤4.8% in the age group 50 to 59 and ≤2.6% in the age group ≥65 years. The incidence of severe limitation of arm movement was ≤3.4% in the age group 50 to 59 years and ≤1.9% in the age group ≥65 years.

5.4.2.2 Systemic Events

5.4.2.2.1 13vPnC in 23vPS-Naïve Subjects Across Studies

The incidence of systemic events reported within 14 days after an initial study vaccination of 13vPnC was assessed in 4 studies.

In studies conducted in naïve subjects, the incidence of fever (ie, temperature ≥38°C) was similar across the studies, ranging from 1.5% to 7.7%, with no apparent differences among the various age groups. In all of these studies, most reports of fever were mild (<38.5°C), and no subjects reported temperatures >40°C. All other types of systemic events were consistently reported at lower incidence in subjects ≥65 years of age than in younger subjects. Among all age groups, the systemic events reported most frequently were fatigue, headache, and new generalized muscle pain.

The incidence for most systemic events was similar between 23vPS-naïve and 23vPS-preimmunized subjects of similar age groups (≥68 years and ≥70 years in studies 3000

and 3005, preimmunized, and ≥65 years in study 3008, naïve) except for new muscle pain which was somewhat higher in one study in preimmunized subjects (36.8%, study 3005) but not the other (25.3%, study 3000), compared to naïve subjects (23.4%).

5.4.2.2.2 Systemic Events: 13vPnC Compared to 23vPS in 23vPS-Naïve Subjects

In subjects 60 to 64 years of age and naïve to 23vPS, all types of systemic events including fever were reported at similar incidence after vaccination with 13vPnC or 23vPS except decreased appetite, aggravated generalized muscle pain, aggravated generalized joint pain, and use of medication to treat fever, which were reported in study 3010 more frequently after 23vPS (Table 5-3).

Table 5-3: Studies 004 and 3010 – Naïve Subjects 60-64 yo Reporting Systemic Events 13vPnC vs 23vPS

	Study 004					Study 3010				
Solicited Systemic Event	13vPnC (%)	23vPS (%)	Difference	(95% CI)	P-value	13vPnC (%)	23vPS (%)	Difference	(95% CI)	P-value
Fever										
Any (≥38 C)	4.0	1.1	2.9	(-0.6, 7.1)	0.096	4.2	1.6	2.6	(-1.6, 6.2)	0.191
Mild (≥38 C but <38.5 C)	4.0	1.1	2.9	(-0.6, 7.1)	0.096	3.8	0.8	3.0	(-0.6, 6.3)	0.087
Moderate (≥38.5 C but <39 C)	0.6	0.0	0.6	(-1.6, 3.2)	0.525	0.8	0.0	0.8	(-2.0, 2.9)	0.455
Severe (≥39 C but ≤40 C)	0.0	0.0	0.0	(-2.1, 2.2)	>.99	0.4	0.8	-0.4	(-3.7, 1.6)	0.693
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-2.1, 2.2)	>.99	0.0	0.0	0.0	(-2.9, 1.6)	>.99
Fatigue	63.2	61.5	1.6	(-6.5, 9.8)	0.717	50.5	49.1	1.3	(-7.9, 10.6)	0.781
Headache	54.0	54.4	-0.5	(-9.1, 8.3)	0.930	49.7	46.1	3.6	(-5.8, 12.9)	0.460
Chills	23.5	24.1	-0.6	(-9.0, 7.8)	0.919	19.9	26.9	-7.0	(-15.9, 1.4)	0.108
Rash	16.5	13.0	3.5	(-3.7, 10.7)	0.344	8.6	13.4	-4.8	(-12.2, 1.7)	0.153
Vomiting	3.9	5.4	-1.5	(-6.2, 3.1)	0.546	3.1	3.1	0.0	(-4.6, 3.6)	>.99
Decreased appetite	21.3	21.7	-0.5	(-8.5, 7.6)	0.937	14.7	23.0	-8.2	(-16.7, -0.4)	0.038
New generalized muscle pain	56.2	57.8	-1.6	(-10.2, 7.0)	0.715	46.9	51.5	-4.6	(-13.9, 4.8)	0.349
Aggravated generalized muscle pain	32.6	37.3	-4.8	(-13.8, 4.2)	0.297	22.0	32.5	-10.4	(-19.6, -1.6)	0.020
New generalized joint pain	24.4	30.1	-5.7	(-14.4, 2.9)	0.195	15.5	23.8	-8.3	(-16.9, -0.4)	0.040
Aggravated generalized joint pain	24.9	21.4	3.5	(-4.7, 11.8)	0.416	14.0	21.1	-7.2	(-15.5, 0.5)	0.068
Use of medication to treat pain	N/A	N/A				31.3	32.7	-1.3	(-10.6, 7.6)	0.779
Use of medication to treat fever	N/A	N/A				8.6	17.5	-8.9	(-16.6, -1.9)	0.012

5.4.2.2.3 Systemic Events: 13vPnC Compared to 23vPS in 23vPS-Preimmunized Subjects - Study 3005

In subjects ≥70 years of age who had previously received 1 dose of 23vPS at least 5 years before vaccination with 13vPnC or 23vPS, the incidence of most systemic events was similar, except fatigue, rash, new generalized muscle pain, and aggravated generalized muscle pain, which were reported at statistically higher incidence after 23vPS compared to 13vPnC (Table 5-4).

The incidence of fever was similar after 13vPnC and 23vPS administration. All fevers were mild after 13vPnC and after 23vPS administration, except for 1 occurrence of severe fever (≥39° C but ≤ 40° C) in the 23vPS group.

These results indicate that subjects preimmunized with 23vPS, 5 years or more before, have significantly higher incidences of some types of systemic events when revaccinated with another dose of 23vPS, compared to vaccination with 13vPnC.

Table 5-4: Study 3005 – Preimmunized Subjects ≥70 yo Reporting Systemic Events 13vPnC vs 23vPS

Event	13vPnC %	23vPS %	Difference	(95% CI)	P-value
Fever					
Any (≥38 C)	1.0	2.3	-1.3	(-3.8, 0.9)	0.253
Mild (≥38 C but <38.5 C)	1.0	2.0	-1.0	(-3.4, 1.2)	0.535
Moderate (≥38.5 C but <39 C)	0.0	0.0	0.0	(-1.2, 1.3)	>.999
Severe (≥39 C but ≤40 C)	0.0	0.3	-0.3	(-1.8, 0.9)	0.509
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-1.2, 1.3)	>.999
Fatigue	34.0	43.3	-9.3	(-16.4, -2.2)	0.011
Headache	23.7	26.0	-2.3	(-8.9, 4.3)	0.510
Chills	7.9	11.2	-3.3	(-8.1, 1.3)	0.162
Rash	7.3	16.4	-9.1	(-14.3, -4.0)	<.001
Vomiting	1.7	1.3	0.4	(-1.9, 2.7)	0.808
Decreased appetite	10.4	11.5	-1.1	(-6.1, 3.9)	0.688
New generalized muscle pain	36.8	44.7	-7.9	(-15.2, -0.6)	0.034
Aggravated generalized muscle pain	20.6	27.5	-6.9	(-13.6, -0.3)	0.039
New generalized joint pain	12.6	14.9	-2.3	(-7.7, 3.1)	0.413
Aggravated generalized joint pain	11.6	16.5	-4.8	(-10.3, 0.6)	0.081
Use of medication to treat pain	22.0	26.6	-4.6	(-11.2, 1.9)	0.169
Use of medication to treat fever	3.0	6.2	-3.2	(-6.8, 0.2)	0.059

5.4.2.2.4 Systemic Events: 13vPnC and 23vPS Administered in a 2-Vaccine Sequence in 23vPS-Naïve Subjects, Study 3010

Systemic events were assessed in subjects 60 to 64 years of age naïve to 23vPS in study 3010. Subjects received either an initial dose of 13vPnC or 23vPS. 13vPnC recipients were vaccinated 1 year later with either 13vPnC or 23vPS. 23vPS recipients were vaccinated 1 year later with 13vPnC.

13vPnC vs 13vPnC/13vPnC: All types of systemic events were reported at similar frequency including fever, which was reported at 7.4% after 13vPnC alone and 1.9% after 13vPnC/13vPnC. All occurrences of fever were either mild or moderate. The most reported types of systemic events after 13vPnC and 13vPnC/13vPnC were fatigue, headache, and new generalized muscle pain (Table 5-5).

13vPnC vs 23vPS/13vPnC: All types of systemic events were reported at similar frequency, including fever which was reported with 4.2% after 13vPnC alone and 0.9% after 23vPS/13vPnC. All occurrences of fever were either mild or moderate except 1 severe fever (≥39° C but ≤ 40° C) after 13vPnC alone. Medication to treat fever was used more frequently at vaccination 2 compared to vaccination 1 (19.4% and 8.6%, respectively). The most frequently reported types of systemic events after 13vPnC and 23vPS/13vPnC were fatigue, headache, and new generalized muscle pain (Table 5-6).

23vPS vs 13vPnC/23vPS: All types of systemic events were reported at similar frequency, except for rash, reported more often after 13vPnC/23vPS (24%) than after 23vPS (13.4%). The incidence of fever was also similar in the 2 groups, ie, 1.6% after 23vPS alone and 3.1% after 13vPnC/23vPS. All occurrences of fever were either mild or moderate except 1 severe fever (≥39° C but ≤40° C) after 23vPS alone. The most frequently reported types of systemic events after 23vPS and 13vPnC/23vPS were fatigue, headache, and new generalized muscle pain (Table 5-7).

13vPnC/13vPnC, 13vPnC/23vPS, and 23vPS/13vPnC comparisons: The incidences for all types of systemic events were similar except for fatigue and rash which were highest after 13vPnC/23vPS (51.9% and 24%, respectively), followed by 13vPnC/13vPnC (39% and 10.5%, respectively), and 23vPS/13vPnC (41.1% and 8.3%, respectively); new generalized muscle pain was highest after 13vPnC/23vPS (61.2%), followed by 13vPnC/13vPnC (50%), and 23vPS/13vPnC (45%); aggravated generalized muscle pain was highest after 13vPnC/23vPS (41.5%) followed by 23vPS/13vPnC (28.7%) and 13vPnC/13vPnC (26.6%). Fever was similar after all 3 sequences, at 1.3% after 13vPnC/13vPnC, 3.1% after 13vPnC/23vPS, and 0.9% after 23vPS/13vPnC. All occurrences of fever were either mild or moderate (Table 5-8).

Table 5-5: Study 3010 – Naïve Subjects 60-64 yo Reporting Systemic Events 13vPnC vs 13vPnC/13vPnC

Event	13vPnC (%)	13vPnC/13vPnC (%)	Difference	(95% CI)
Fever				
Any (≥38°C)	7.4	1.9	-5.6	(-13.8, 3.1)
Mild (≥38°C but <38.5°C)	7.4	0.0	-7.4	(-14.7, 0.5)
Moderate (≥38.5°C but <39°C)	0.0	1.9	1.9	(-3.1, 6.7)
Severe (≥39°C but ≤40°C)	0.0	0.0	0	(-3.5, 3.5)
Potentially life threatening (>40°C)	0.0	0.0	0	(-3.5, 3.5)
Fatigue	56.6	43.4	-13.2	(-25.1, -0.6)
Headache	52.6	44.7	-7.9	(-19.1, 3.7)
Chills	18.0	19.7	1.6	(-8.2, 11.4)
Rash	8.3	10.0	1.7	(-9.3, 12.6)
Vomiting	7.1	3.6	-3.6	(-12.3, 5.4)
Decreased appetite	13.1	21.3	8.2	(-3.5, 19.4)
New generalized muscle pain	47.6	51.2	3.6	(-10.2, 17.1)
Aggravated generalized muscle pain	26.5	30.9	4.4	(-8.8, 17.4)
New generalized joint pain	14.5	16.1	1.6	(-9.9, 13.0)
Aggravated generalized joint pain	16.1	19.4	3.2	(-9.5, 15.7)
Use of medication to treat pain	26.9	31.3	4.5	(-8.3, 17.0)
Use of medication to treat fever	3.4	15.3	11.9	(2.9, 20.1)
Any systemic event	78.4	73.5	-4.9	(-14.7, 5.1)

Table 5-6: Study 3010 – Naïve Subjects 60-64 yo Reporting Systemic Events 23vPS/13vPnC vs 13vPnC

Event	13vPnC (%)	23vPS/13vPnC (%)	Difference	(95% CI)	P-value
Fever					
Any (≥38 C)	4.2	0.9	3.3	(-0.6, 6.8)	0.085
Mild (≥38 C but <38.5 C)	3.8	0.9	3.0	(-1.0, 6.3)	0.113
Moderate (≥38.5 C but <39 C)	0.8	0.0	0.8	(-2.3, 2.9)	0.501
Severe (≥39 C but ≤40 C)	0.4	0.0	0.4	(-2.6, 2.3)	0.823
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-3.2, 1.6)	>0.99
Fatigue	50.5	41.1	9.3	(-0.6, 19.0)	0.066
Headache	49.7	40.3	9.4	(-0.5, 19.1)	0.065
Chills	19.9	19.7	0.2	(-8.6, 8.3)	0.983
Rash	8.6	8.3	0.3	(-6.4, 6.0)	0.987
Vomiting	3.1	6.8	-3.7	(-9.8, 1.0)	0.116
Decreased appetite	14.7	13.0	1.7	(-6.2, 8.7)	0.671
New generalized muscle pain	46.9	45.0	1.9	(-7.8, 11.5)	0.708
Aggravated generalized muscle pain	22.0	28.7	-6.6	(-16.0, 2.2)	0.142
New generalized joint pain	15.5	19.5	-4.1	(-12.7, 3.7)	0.324
Aggravated generalized joint pain	14.0	21.4	-7.4	(-16.0, 0.6)	0.072
Use of medication to treat pain	31.3	20.3	11.0	(1.8, 19.5)	0.020
Use of medication to treat fever	8.6	19.4	-10.7	(-19.1, -3.2)	0.004
Any systemic event	74.9	62.7	12.2	(3.8, 20.8)	0.003

Table 5-7: Study 3010 – Naïve Subjects 60-64 yo Reporting Systemic Events 23vPS vs 13vPnC/23vPS

Event	23vPS (%)	13vPnC/23vPS (%)	Difference	(95% CI)	P-value
Fever					
Any (≥38°C)	1.6	3.1	1.5	(-2.8, 6.3)	0.539
Mild (≥38°C but <38.5°C)	0.8	3.1	2.3	(-1.6, 7.0)	0.251
Moderate (≥38.5°C but <39°C)	0.0	0.0	0.0	(-2.9, 2.9)	>.999
Severe (≥39°C but ≤40°C)	0.8	0.0	-0.8	(-4.3, 2.1)	0.529
Potentially life threatening (>40°C)	0.0	0.0	0.0	(-2.9, 2.9)	>.999
Fatigue	49.1	51.9	2.8	(-7.8, 13.3)	0.614
Headache	46.1	49.7	3.6	(-7.0, 14.2)	0.521
Chills	26.9	29.0	2.1	(-8.1, 12.4)	0.692
Rash	13.4	24.0	10.5	(1.0, 19.8)	0.025
Vomiting	3.1	4.6	1.5	(-3.6, 7.0)	0.561
Decreased appetite	23.0	17.0	-6.0	(-15.3, 3.4)	0.213
New generalized muscle pain	51.5	61.2	9.7	(-0.6, 19.9)	0.064
Aggravated generalized muscle pain	32.5	41.5	9.0	(-1.7, 19.7)	0.100
New generalized joint pain	23.8	25.5	1.7	(-8.2, 11.6)	0.754
Aggravated generalized joint pain	21.1	17.5	-3.6	(-13.0, 5.6)	0.459
Use of medication to treat pain	32.7	46.2	13.6	(2.9, 24.2)	0.013
Use of medication to treat fever	17.5	17.4	-0.1	(-9.1, 8.8)	>.999
Any systemic event	78.2	78.8	0.6	(-7.3, 8.6)	0.894

Table 5-8: Study 3010 – Naïve Subjects 60-64 yo Reporting Systemic Events at Year 1 13vPnC/13vPnC vs 13vPnC/23vPS vs 23vPS/13vPnC

Event	13vPnC/13vPnC %	13vPnC/23vPS %	23vPS/13vPnC %	P-value
Fever				
Any (≥38 C)	1.3	3.1	0.9	.0651, >.99, 0.373
Mild (≥38 C but <38.5 C)	0	3.1	0.9	0.300, >.99, 0.373
Moderate (≥38.5 C but <39 C)	1.3	0	0	0.386, 0.410, N/A
Severe (≥39 C but ≤40 C)	0	0	0	N/A, N/A, N/A
Potentially life threatening (>40 C)	0	0	0	N/A, N/A, N/A
Fatigue	39.0	51.9	41.1	0.047, 0.790, 0.058
Headache	41.7	49.7	40.3	0.252, 0.893, 0.110
Chills	18.9	29.0	19.7	0.094, >.99, 0.074
Rash	10.5	24.0	8.3	0.015, 0.630, <.001
Vomiting	3.7	4.6	6.8	>.99, 0.530, 0.584
Decreased appetite	18.0	17.0	13.0	0.860, 0.337, 0.394
New generalized muscle pain	50.0	61.2	45.0	0.069, 0.451, 0.003
Aggravated generalized muscle pain	26.6	41.5	28.7	0.022, 0.766, 0.022
New generalized joint pain	14.9	25.5	19.5	0.073, 0.467, 0.256
Aggravated generalized joint pain	17.6	17.5	21.4	>.99, 0.608, 0.446
Use of medication to treat pain	26.9	46.2	20.3	0.002, 0.262, <.001
Use of medication to treat fever	13.8	17.4	19.4	0.580, 0.354, 0.752
Any systemic event	70.9	78.8	62.7	0.110, 0.164, <.001

p-value Fisher exact test 2-sided
13vPnC/13vPnC vs 13vPnC/23vPS; 13vPnC/13vPnC vs 23vPS/13vPnC; 13vPnC/23vPS vs 23vPS/13vPnC SA-013

5.4.2.2.5 Systemic Events: 13vPnC and 23vPS Administered in a 2-Vaccine Sequence in 23vPS-Naïve Subjects, Study 004 Extension

Data from the 004 extension study on solicited systemic events after a second dose of vaccine (13vPnC/23vPS, 13vPnC/13vPnC, and 23vPS/23vPS) have recently become available, and a clinical study report including these data was provided to the FDA on August 31, 2011. This report provides information on administration of these vaccines with a 3.5 to 4-year interval between doses, for those subjects who received both doses.

Systemic events after the second dose of 13vPnC were comparable to those after the first dose in both the 60 to 64-year-old and 50 to 59-year-old cohorts, with no statistical increases after the

second dose (Table 5-9 and Table 5-10). Likewise, systemic events after 23vPS in the sequence 13vPnC/23vPS were comparable to those after the first 13vPnC dose (Table 5-11).

Table 5-9: Study 004 (Ext) – Naïve Subjects 60-64 yo Reporting Systemic Events 13vPnC vs 13vPnC/13vPnC

Event	13vPnC %	13vPnC/13vPnC %	Difference	(95% CI)
Fever				
Any (≥38 C)	0.0	0.0	0.0	(-5.9, 5.9)
Mild (≥38 C but <38.5 C)	0.0	0.0	0.0	(-5.9, 5.9)
Moderate (≥38.5 C but <39 C)	0.0	0.0	0.0	(-5.9, 5.9)
Severe (≥39 C but ≤40 C)	0.0	0.0	0.0	(-5.9, 5.9)
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-5.9, 5.9)
Fatigue	62.3	49.1	-13.2	(-27.5, 2.0)
Headache	51.2	37.2	-14.0	(-27.2, 0.6)
Chills	22.2	22.2	0.0	(-13.6, 13.6)
Rash	12.1	24.2	12.1	(-2.9, 25.8)
Vomiting	3.2	6.5	3.2	(-5.3, 11.4)
Decreased appetite	20.6	14.7	-5.9	(-21.8, 10.7)
New generalized muscle pain	47.7	50.0	2.3	(-15.9, 20.2)
Aggravated generalized muscle pain	22.9	22.9	0.0	(-19.1, 19.1)
New generalized joint pain	21.6	24.3	2.7	(-13.3, 18.4)
Aggravated generalized joint pain	19.4	16.7	-2.8	(-18.9, 13.7)
Any systemic event	79.1	77.6	-1.5	(-13.5, 10.6)

Table 5-10: Study 004 (Ext) – Naïve Subjects 50-59 yo Reporting Systemic Events 13vPnC vs 13vPnC/13vPnC

Event	13vPnC %	13vPnC/13vPnC %	Difference	(95% CI)
Fever				
Any (≥38 C)	0.0	2.6	2.6	(-4.4, 9.4)
Mild (≥38 C but <38.5 C)	0.0	2.6	2.6	(-4.4, 9.4)
Moderate (≥38.5 C but <39 C)	0.0	0.0	0.0	(-5.0, 5.0)
Severe (≥39 C but ≤40 C)	0.0	0.0	0.0	(-5.0, 5.0)
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-5.0, 5.0)
Fatigue	65.6	65.6	0.0	(-10.7, 10.7)
Headache	72.7	61.4	-11.4	(-21.3, -0.9)
Chills	24.5	22.6	-1.9	(-15.1, 11.5)
Rash	9.8	7.3	-2.4	(-15.2, 10.5)
Vomiting	7.1	7.1	0.0	(-10.0, 10.0)
Decreased appetite	28.3	26.4	-1.9	(-15.1, 11.5)
New generalized muscle pain	69.0	67.8	-1.1	(-12.8, 10.5)
Aggravated generalized muscle pain	42.6	36.1	-6.6	(-20.5, 7.8)
New generalized joint pain	35.2	31.5	-3.7	(-18.0, 10.8)
Aggravated generalized joint pain	25.0	25.0	0.0	(-14.1, 14.1)
Any systemic event	92.0	88.3	-3.6	(-8.8, 1.6)

Table 5-11: Study 004 (Ext) – Naïve Subjects 60-64 yo Reporting Systemic Events 13vPnC vs 13vPnC/23vPS

Event	13vPnC %	13vPnC/23vPS %	Difference	(95% CI)
Fever				
Any (≥38 C)	0.0	4.8	4.8	(-7.6, 16.3)
Mild (≥38 C but <38.5 C)	0.0	4.8	4.8	(-7.6, 16.3)
Moderate (≥38.5 C but <39 C)	0.0	0.0	0.0	(-8.9, 8.9)
Severe (≥39 C but ≤40 C)	0.0	0.0	0.0	(-8.9, 8.9)
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-8.9, 8.9)
Fatigue	68.6	68.6	0.0	(-13.3, 13.3)
Headache	54.8	52.4	-2.4	(-18.9, 14.4)
Chills	33.3	26.7	-6.7	(-24.5, 12.0)
Rash	27.6	17.2	-10.3	(-29.4, 10.0)
Vomiting	0.0	4.8	4.8	(-7.6, 16.3)
Decreased appetite	31.0	34.5	3.4	(-12.2, 18.7)
New generalized muscle pain	56.5	71.7	15.2	(-0.1, 29.3)
Aggravated generalized muscle pain	32.3	38.7	6.5	(-9.5, 21.6)
New generalized joint pain	31.0	20.7	-10.3	(-21.9, 2.5)
Aggravated generalized joint pain	20.8	25.0	4.2	(-11.2, 18.9)
Any systemic event	87.5	82.8	-4.7	(-15.6, 6.5)

The comparable reaction rates seen after a second dose in the sequence 13vPnC/13vPnC or 13vPnC/23vPS compared to the first dose of 13vPnC contrasted somewhat with the observations after 23vPS/23vPS. Although systemic events after a second dose of 23vPS were generally comparable to those after the first 23vPS dose, rash and muscle pain were statistically more frequent after the second dose (Table 5-12). Rates after 13vPnC/23vPS were comparable and not statistically different from rates after 23vPS/23vPS (Table 5-13). Rates of systemic events after 13vPnC/13vPnC were generally comparable or lower than those after 23vPS/23vPS, and statistically so (marginally) for headache (-15.9%; 95% CI:-30.8%, -0.1%) (Table 5-14). Findings support administration of 13vPnC/13vPnC or 13vPnC/23vPS, with a favorable or comparable systemic reaction profile, respectively, compared to 23vPS/23vPS.

Table 5-12: Study 004 (Ext) – Naïve Subjects 60-64 yo Reporting Systemic Events 23vPS vs 23vPS/23vPS

Event	23vPS %	23vPS/23vPS %	Difference	(95% CI)
Fever				
Any (≥38 C)	9.1	2.3	-6.8	(-16.8, 3.7)
Mild (≥38 C but <38.5 C)	2.3	2.3	0.0	(-7.5, 7.5)
Moderate (≥38.5 C but <39 C)	0.0	0.0	0.0	(-4.4, 4.4)
Severe (≥39 C but ≤40 C)	0.0	0.0	0.0	(-4.4, 4.4)
Potentially life threatening (>40 C)	6.8	0.0	-6.8	(-14.8, 1.8)
Fatigue	64.9	56.4	-8.5	(-19.2, 2.5)
Headache	61.0	57.3	-3.7	(-15.4, 8.3)
Chills	25.9	32.8	6.9	(-7.5, 20.8)
Rash	9.1	32.7	23.6	(9.5, 36.1)
Vomiting	0.0	2.3	2.3	(-3.8, 8.2)
Decreased appetite	19.6	21.6	2.0	(-9.8, 13.6)
New generalized muscle pain	57.9	70.5	12.6	(2.2, 22.6)
Aggravated generalized muscle pain	25.0	40.0	15.0	(0.1, 28.9)
New generalized joint pain	25.0	23.2	-1.8	(-12.4, 9.0)
Aggravated generalized joint pain	11.3	17.0	5.7	(-5.7, 16.6)
Any systemic event	84.8	86.4	1.5	(-4.9, 7.9)

Table 5-13: Study 004 (Ext) – Naïve Subjects 60-64 yo Reporting Systemic Events 13vPnC/23vPS vs 23vPS/23vPS

Event	13vPnC/23vPS %	23vPS/23vPS %	Difference	(95% CI)	P-value
Fever					
Any (≥38 C)	4.7	2.5	2.1	(-5.4, 13.1)	0.577
Mild (≥38 C but <38.5 C)	2.4	2.5	-0.2	(-7.4, 10.1)	>.99
Moderate (≥38.5 C but <39 C)	2.4	0.0	2.4	(-2.7, 12.6)	0.322
Severe (≥39 C but ≤40 C)	0.0	0.0	0.0	(-5.1, 8.6)	>.99
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-5.1, 8.6)	>.99
Fatigue	63.2	57.6	5.6	(-9.2, 19.8)	0.479
Headache	50.0	54.2	-4.2	(-19.5, 11.1)	0.603
Chills	33.9	34.3	-0.4	(-15.6, 15.7)	0.977
Rash	18.4	32.6	-14.3	(-28.1, 1.4)	0.075
Vomiting	4.7	1.3	3.4	(-3.2, 14.2)	0.406
Decreased appetite	31.5	23.7	7.8	(-7.0, 23.5)	0.315
New generalized muscle pain	65.2	67.6	-2.5	(-17.1, 11.3)	0.747
Aggravated generalized muscle pain	41.4	39.6	1.8	(-14.0, 18.0)	0.833
New generalized joint pain	24.5	23.1	1.5	(-12.6, 17.0)	0.852
Aggravated generalized joint pain	22.4	17.6	4.9	(-8.7, 20.2)	0.503
Any systemic event	80.7	85.2	-4.5	(-15.4, 5.3)	0.401

Table 5-14: Study 004 (Ext) – Naïve Subjects 60-64 yo Reporting Systemic Events 13vPnC/13vPnC vs 23vPS/23vPS

Event	13vPnC/13vPnC %	23vPS/23vPS %	Difference	(95% CI)	P-value
Fever					
Any (≥38 C)	2.1	2.5	-0.4	(-7.3, 8.3)	>.99
Mild (≥38 C but <38.5 C)	0.0	2.5	-2.5	(-9.0, 5.2)	0.373
Moderate (≥38.5 C but <39 C)	2.1	0.0	2.1	(-3.3, 11.1)	0.360
Severe (≥39 C but ≤40 C)	0.0	0.0	0.0	(-4.8, 7.5)	>.99
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-4.8, 7.5)	>.99
Fatigue	50.7	57.6	-6.9	(-21.5, 7.9)	0.376
Headache	38.3	54.2	-15.9	(-30.8, -0.1)	0.049
Chills	23.1	34.3	-11.3	(-25.5, 4.4)	0.159
Rash	23.5	32.6	-9.1	(-23.6, 6.9)	0.288
Vomiting	8.3	1.3	7.1	(-0.4, 18.8)	0.063
Decreased appetite	21.2	23.7	-2.5	(-16.1, 12.7)	0.820
New generalized muscle pain	55.0	67.6	-12.6	(-27.6, 2.3)	0.090
Aggravated generalized muscle pain	27.5	39.6	-12.2	(-27.1, 4.3)	0.145
New generalized joint pain	18.9	23.1	-4.2	(-17.5, 10.5)	0.641
Aggravated generalized joint pain	13.7	17.6	-3.9	(-15.9, 10.1)	0.737
Any systemic event	80.0	85.2	-5.2	(-16.4, 4.7)	0.329

5.4.2.2.6 Systemic Events: 13vPnC and 23vPS Administered in a 2-Vaccine Sequence in 23vPS-Preimmunized Subjects

Systemic events were assessed in subjects ≥70 years of age preimmunized with 23vPS five years or more before. They received either an initial dose of 13vPnC or 23vPS. All study subjects were vaccinated 1 year later with 13vPnC.

13vPnC vs 13vPnC/13vPnC: All types of systemic events were reported at similar frequency including fever, which was reported at 1.7% after 13vPnC alone and 1.1% after 13vPnC/13vPnC. In the 13vPnC group, all occurrences of fever were mild. In the 13vPnC/13vPnC group 1 case of severe fever (≥39° C but ≤ 40° C) was reported. The most reported types of systemic events after 13vPnC and 13vPnC/13vPnC were new generalized muscle pain and fatigue (Table 5-15).

13vPnC vs 23vPS/13vPnC: All types of systemic events were reported at similar frequency, including fever which was reported at 1% after 13vPnC alone and 1.8% after 23vPS/13vPnC.

In both groups, most cases of fever were mild. After 23vPS/13vPnC one case of severe fever was reported. Medication to treat fever was more frequently reported when 23vPS/13vPnC was given (7.4%) than when 13vPnC alone was given (3%). Medication to treat pain was reported more often after 13vPnC alone (22.0%) than after 23vPS/13vPnC (15.4%).

The most frequently reported types of systemic events after 13vPnC and 23vPS/13vPnC were new generalized muscle pain and fatigue (Table 5-16).

13vPnC/13vPnC vs 23vPS/13vPnC: All types of systemic events, except for vomiting, were reported at similar frequency. The incidence of fever was 2.6% after 13vPnC/13vPnC and 1.8% after 23vPS/13vPnC, and most fevers were mild and moderate. One (1) subject in each group reported fever ≥39°C but ≤ 40°C and 1 subject reported fever >40°C after 13vPnC/13vPnC. The most frequently reported types of systemic events in both study groups were new generalized muscle pain and fatigue (Table 5-17).

Table 5-15: Study 3005 – Preimmunized Subjects ≥70 yo Reporting Systemic Events 13vPnC vs 13vPnC/13vPnC

Event	13vPnC %	13vPnC/13vPnC %	Difference	(95% CI)
Fever				
Any (≥38°C)	1.7	1.1	-0.6	(-3.2, 2.1)
Mild (≥38°C but <38.5°C)	1.7	0.6	-1.1	(-3.6, 1.3)
Moderate (≥38.5°C but <39°C)	0.0	0.0	0	(-1.1, 1.1)
Severe (≥39°C but ≤40°C)	0.0	0.6	0.6	(-1.0, 2.1)
Potentially life threatening (>40°C)	0.0	0.0	0	(-1.1, 1.1)
Fatigue	33.5	28.4	-5.1	(-11.5, 1.4)
Headache	23.0	19.0	-4	(-10.0, 2.1)
Chills	9.3	4.4	-4.9	(-9.6, -0.2)
Rash	8.2	6.0	-2.2	(-6.3, 1.9)
Vomiting	1.1	0.0	-1.1	(-3.0, 0.8)
Decreased appetite	8.4	7.9	-0.5	(-4.9, 3.8)
New generalized muscle pain	37.9	35.6	-2.3	(-9.7, 5.2)
Aggravated generalized muscle pain	20.7	16.2	-4.5	(-11.3, 2.3)
New generalized joint pain	11.2	7.5	-3.7	(-8.8, 1.3)
Aggravated generalized joint pain	11.2	10.1	-1.1	(-6.4, 4.3)
Use of medication to treat pain	21.8	18.4	-3.4	(-9.9, 3.1)
Use of medication to treat fever	3.3	2.2	-1.1	(-4.6, 2.4)
Any systemic event	60.2	56.4	-3.9	(-10.7, 3.0)

Table 5-16: Study 3005 – Preimmunized Subjects ≥70 yo Reporting Systemic Events 13vPnC vs 23vPS/13vPnC

Event	13vPnC %	23vPS/13vPnC %	Difference	(95% CI)	P-value
Fever					
Any (≥38 C)	1.0	1.8	0.8	(-1.4, 3.6)	0.577
Mild (≥38 C but <38.5 C)	1.0	1.8	0.8	(-1.4, 3.6)	0.577
Moderate (≥38.5 C but <39 C)	0.0	0.0	0.0	(-1.3, 1.7)	>.999
Severe (≥39 C but ≤40 C)	0.0	0.5	0.5	(-0.9, 2.5)	0.421
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-1.3, 1.7)	>.999
Fatigue	34.0	34.3	0.3	(-7.2, 8.0)	0.933
Headache	23.7	22.6	-1.1	(-8.0, 5.9)	0.760
Chills	7.9	9.9	2.0	(-2.9, 7.2)	0.424
Rash	7.3	7.1	-0.2	(-4.7, 4.6)	0.959
Vomiting	1.7	3.1	1.4	(-1.3, 4.7)	0.425
Decreased appetite	10.4	7.4	-3.0	(-7.8, 2.0)	0.270
New generalized muscle pain	36.8	35.0	-1.8	(-9.5, 5.9)	0.648
Aggravated generalized muscle pain	20.6	21.0	0.3	(-6.5, 7.2)	0.923
New generalized joint pain	12.6	12.0	-0.6	(-6.2, 5.2)	0.840
Aggravated generalized joint pain	11.6	11.7	0.1	(-5.4, 5.8)	0.986
Use of medication to treat pain	22.0	15.4	-6.6	(-13.0, 0.0)	0.049
Use of medication to treat fever	3.0	7.4	4.4	(0.5, 8.7)	0.022
Any systemic event	60.3	58.2	-2.1	(-9.6, 5.3)	0.582

Table 5-17: Study 3005 – Preimmunized Subjects ≥70 yo Reporting Systemic Events After Vaccination 2 (Year 1)

Event	13vPnC/13vPnC (%)	23vPS/13vPnC (%)	Difference	(95% CI)	P-Value
Fever					
Any (≥38 C)	2.6	1.8	0.8	(-2.2, 4.1)	0.581
Mild (≥38 C but <38.5 C)	0.9	1.8	-0.9	(-3.7, 1.6)	0.529
Moderate (≥39 C but ≤39 C)	0.9	0.0	0.9	(-0.8, 3.2)	0.217
Severe (≥39 C but ≤40 C)	0.4	0.5	0.0	(-2.1, 2.1)	>.999
Potentially life threatening (>40 C)	0.4	0.0	0.4	(-1.3, 2.5)	0.512
Fatigue	28.6	34.3	-5.7	(-13.7, 2.3)	0.163
Headache	19.1	22.6	-3.5	(-10.7, 3.7)	0.348
Chills	7.3	9.9	-2.6	(-7.9, 2.6)	0.363
Rash	6.0	7.1	-1.0	(-5.8, 3.6)	0.718
Vomiting	0.4	3.1	-2.7	(-5.8, -0.2)	0.032
Decreased appetite	8.9	7.4	1.5	(-3.6, 6.6)	0.594
New generalized muscle pain	34.6	35.0	-0.4	(-8.6, 7.8)	0.955
Aggravated generalized muscle pain	18.0	21.0	-3.0	(-10.1, 4.0)	0.407
New generalized joint pain	10.5	12.0	-1.5	(-7.3, 4.3)	0.644
Aggravated generalized joint pain	12.6	11.7	0.9	(-5.2, 6.9)	0.797
Use of medication to treat pain	19.0	15.4	3.6	(-3.2, 10.4)	0.296
Use of medication to treat fever	3.9	7.4	-3.5	(-8.0, 0.8)	0.126
Any systemic event	55.5	58.2	-2.7	(-10.7, 5.4)	0.524

5.4.2.2.7 Systemic Events: 13vPnC with Concomitant Administration of Trivalent Influenza Vaccine (TIV)

After concomitant administration of 13vPnC+TIV in subjects 50 to 59 years of age, similar frequencies for all systemic events were observed compared to 13vPnC administered alone, except for a trend for increased fatigue with 58.1% after 13vPnC+TIV and 51.8% after 13vPnC alone and statistically higher frequency of headache with 65.9% after 13vPnC+TIV and 50.9% after 13vPnC alone. The most often observed systemic reactions (after 13vPnC+TIV and after 13vPnC alone, respectively) were: headache (65.9% and 50.9%), new muscle pain (65.5% and 59.1%), and fatigue (58.1% and 51.8%). Fever was noted in 3.4% (after 13vPnC+TIV) and 2.5% of cases (after 13vPnC alone), most incidences being mild or moderate.

After concomitant administration of 13vPnC+TIV in subjects ≥65 years of age, similar frequencies for most systemic reactions were observed compared to 13vPnC administered alone . Statistically significantly higher rates were noted after 13vPnC+TIV compared to 13vPnC alone for fatigue (37.4% and 28.5%), headache (32.6% and 24.7%), chills (13.8% and 9.1%) decreased appetite (16.9% and 11.2%), new joint pain (16.2% and 11.5%), and aggravated generalized joint pain (15.7% and 8.6%).

The most often observed systemic reactions (after 13vPnC+TIV and after 13vPnC alone, respectively) were: fatigue (37.4% and 28.5%), headache (32.6% and 24.7%), and new muscle pain (26.9% and 23.4%).

Fever was noted in 5.3% (after 13vPnC+TIV) and 4.2% of cases (after 13vPnC alone). All occurrences of fever were mild or moderate .

Incidences for all types of systemic events were higher in the younger (50 to 59 years) compared to the older (≥65 years) age group, except for fever which was similar in both age groups.

After concomitant administration of 13vPnC+TIV in subjects 50 to 59 years of age, statistically significantly higher incidences for all types of systemic events were observed compared to TIV (+placebo) alone, except for fatigue, vomiting and aggravated generalized joint pain, which were similar in both groups (Table 5-18). Systemic events after 13vPnC+TIV ranged from 5.3% (vomiting) to 65.9% (headache), and after TIV alone from 3.4% (vomiting) to 56.5% (headache).

The most frequently reported systemic events were headache (65.9% and 56.5%), new muscle pain (65.5% and 37.7%), and fatigue (58.1% and 52.4%) after 13vPnC+TIV and TIV alone, respectively.

Fever was generally similar in both groups after 13vPnC+TIV and TIV alone. More moderate fevers (≥38.5° C but <39°C) were reported after 13vPnC+TIV compared to TIV alone (1.5% and 0%).

After concomitant administration of 13vPnC+TIV in subjects ≥65 years of age, similar frequencies for all systemic reactions were observed compared to TIV administered alone, except for chills (13.8% and 9.1%), rash (6.9% and 3.4%), and new muscle pain (26.9% and 16.7%), which were statistically significantly higher in the 13vPnC+TIV group compared to TIV alone (Table 5-19). The most frequently reported systemic events were fatigue (37.4% and 31.9%), headache (32.6% and 29.7%), and new muscle pain (26.9% and 16.7%) after 13vPnC+TIV compared to TIV alone, respectively.

Fever was similar in both groups after 13vPnC+TIV and TIV alone. Most occurrences of fever were mild to moderate.

When the 2 age groups (50 to 59 years and ≥65 years) were compared, the occurrences of fever were similar after 13vPnC+TIV; however, all other systemic events were higher in the younger compared to the older age group. The same observation was made for TIV alone: higher incidences for all systemic events, except for fever (similar), were observed in the younger relative to the older age group.

Table 5-18: Study 3001 – Naïve Subjects 50-59 yo Reporting Systemic Events 13vPnC+TIV vs Placebo+TIV

Event	13vPnC+ TIV %	TIV %	Difference	(95% CI)	P-value
Fever					
Mild (≥38 C but <38.5 C)	1.5	1.2	0.4	(-2.0, 2.8)	0.804
Moderate (≥38.5 C but <39 C)	1.5	0.0	1.5	(0.0, 3.9)	0.049
Severe (≥39 C but ≤40 C)	0.4	0.0	0.4	(-1.1, 2.1)	0.511
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-1.4, 1.5)	>.99
Fatigue	58.1	52.4	5.7	(-1.4, 12.8)	0.119
Headache	65.9	56.5	9.4	(2.5, 16.2)	0.008
Chills	31.4	21.0	10.4	(3.4, 17.4)	0.004
Rash	12.6	4.9	7.7	(2.5, 12.6)	0.002
Vomiting	5.3	3.4	1.8	(-1.8, 5.6)	0.316
Decreased appetite	30.2	22.6	7.6	(0.6, 14.5)	0.034
New muscle pain	65.5	37.7	27.7	(20.5, 34.7)	<0.001
Aggravated generalized muscle pain	34.7	24.1	10.6	(3.3, 17.8)	0.004
New joint pain	33.0	24.7	8.3	(1.1, 15.6)	0.024
Aggravated generalized joint pain	21.2	18.0	3.3	(-3.3, 9.8)	0.328
Use of medication to treat pain	39.3	24.5	14.8	(7.4, 22.1)	<0.001
Use of medication to treat fever	22.8	13.9	8.9	(2.6, 15.3)	0.006

Table 5-19: Study 3008 – Naïve Subjects ≥65 yo Reporting Systemic Events 13vPnC+TIV vs Placebo+TIV

Event	13vPnC +TIV %	TIV %	Difference	(95% CI)	P-value
Fever					
Mild (≥38 C but <38.5 C)	3.0	1.9	1.2	(-1.0, 3.4)	0.288
Moderate (≥38.5 C but <39 C)	1.4	1.2	0.2	(-1.5, 2.0)	0.827
Severe (≥39 C but ≤40 C)	0.0	0.2	-0.2	(-1.3, 0.6)	0.508
Potentially life threatening (>40 C)	0.0	0.0	0.0	(-0.9, 0.9)	>.99
Fatigue	37.4	31.9	5.5	(-0.5, 11.5)	0.075
Headache	32.6	29.7	2.9	(-3.0, 8.9)	0.339
Chills	13.8	9.1	4.7	(0.5, 8.9)	0.029
Rash	6.9	3.4	3.5	(0.4, 6.6)	0.021
Vomiting	3.0	3.4	-0.4	(-2.9, 2.0)	0.804
Decreased appetite	16.9	14.6	2.3	(-2.5, 7.1)	0.350
New muscle pain	26.9	16.7	10.3	(4.9, 15.6)	<.001
Any aggravated muscle pain	18.7	14.0	4.7	(-0.2, 9.6)	0.058
New joint pain	16.2	13.1	3.1	(-1.6, 7.7)	0.195
Any aggravated joint pain	15.7	13.0	2.7	(-1.9, 7.4)	0.245
Use of medication to treat pain	10.7	10.5	0.1	(-4.0, 4.2)	0.987
Use of medication to treat fever	4.8	5.0	-0.2	(-3.2, 2.7)	0.926

5.4.3 Spontaneously Reported Adverse Events

5.4.3.1 Adverse Events After 13vPnC Across Studies

The incidence of adverse events (AEs) reported within 1 month after an initial study vaccination with 13vPnC was similar across all 6 studies, ranging from 11.4% to 19.2%, and did not appear to be affected by subject age or 23vPS immunization status (ie, naïve or preimmunized subjects). The overall incidence of AEs occurring after administration of 13vPnC in subjects 50 to 64 years of age (studies 004, 3001, 3010) was similar to the incidence in subjects ≥65 years of age (studies 3000, 3005, 3008). Likewise, the incidence of AEs in subjects naïve to 23vPS (004, 3001, 3008, and 3010) was similar to the incidence in subjects who had received 23vPS at least 3 years prior to study entry (studies 3000 and 3005).

Across the studies, the types of AEs reported most frequently were infections and infestations (4.1% to 8.6% of subjects), musculoskeletal and connective tissue disorders (1.6% to 4.1%), general disorders and administration site conditions (0.6% to 3.1%), and respiratory, thoracic, and mediastinal disorders (0.4% to 2.3%). There were no apparent differences in the incidence or types of AEs reported among the various age groups. In all studies, the AEs reported were generally the types of diseases and conditions often observed in adults in these age groups.
AEs occurring after administration of 13vPnC and considered at least possibly related to study vaccine were also reported at similar frequencies across the 6 primary studies (1.1% to 3.1% of subjects) regardless of subject age or 23vPS vaccination status. The types of AEs most often reported as related to study vaccine were administration site conditions.

Only serious AEs (SAEs) and newly diagnosed chronic medical conditions were to be reported at the 6-month follow-up telephone contact. The incidence of AEs reported at the 6-month follow up ranged from 1.5% to 17.3%, with no apparent trends related to subject age. Two (2) AEs reported at the 6-month follow-up contact were considered related to study vaccine; one case with arthralgia, bursitis, and tendonitis, and one case of Guillain-Barré Syndrome (see details under Section 5.4.3.7).

5.4.3.2 Adverse Events in 23vPS-Naïve Subjects

In 23vPS-naïve subjects 60 to 64 years of age the overall incidence of AEs after 13vPnC was similar to the incidence of AEs after 23vPS (studies 004, 3010). The incidence of AEs reported at the 6-month follow-up contact was also similar after 13vPnC and 23vPS.

When the 3 vaccine sequences, 13vPnC/13vPnC, 13vPnC/23vPS, and 23vPS/13vPnC, were compared in naïve subjects 60 to 64 years of age the incidences of AEs after each vaccine sequence were similar (MedDRA, SOCs or preferred terms), ranging from 13.8% to 19.1%. AEs related to vaccine were reported ≤1.9% of subjects in each sequence (study 3010). The incidences of AEs after vaccination 2 reported at the 6-month follow up telephone contact were also similar (study 3010). For all 3 sequences the most frequently reported AEs were infections and infestations (4.0% to 7.5%). None of the AEs reported at the 6-month follow up after vaccination was considered vaccine-related.

When the 3 vaccine sequences were compared to the initial vaccine (13vPnC or 23vPS), no clinically relevant differences of the AEs reported were found (MedDRA, SOCs, preferred terms). The most frequently reported AEs were infections and infestations (4% to 13.1%). The incidence of vaccine-related AEs was also similar between vaccination 2 and vaccination 1 (study 3010).

Recently available data on adverse events occurring in the 004 extension study were included in the clinical study report submitted to the FDA on August 31, 2011. In cohort 1, comparisons of AEs after vaccination 2 were made for the following groups: 13vPnC/23vPS vs 23vPS/23vPS, 13vPnC/13vPnC vs 23vPS/23vPS, and the 13vPnC/13vPnC vs 13vPnC/23vPS. The most frequent category of AEs in each vaccine group was infections and infestations, which occurred in 8.3%, 9.3%, and 8.5% of subjects for the 13vPnC/13vPnC, 13vPnC/23vPS, and 23vPS/23vPS groups. In all cohort 1 comparisons, there were no statistically significant differences for the incidences of any AE, for the categories of AE, or for individual preferred terms. The incidences of AEs were also compared between the 13vPnC/13vPnC group in cohort 1 and cohort 2 (13vPnC/13vPnC). The percentage of subjects reporting any AEs within approximately 1 month after vaccination 2 was higher for subjects in the 13vPnC/13vPnC group in cohort 1 (21.3%) compared to that in the 13vPnC/13vPnC group in cohort 2 (10.7%); although this difference was

statistically significant (p=0.011), review of the AEs does not suggest any clinically relevant differences. Events were primarily due to diseases typically observed in adults 50 years and above with a somewhat higher incidence in the older age group.

5.4.3.3 Adverse Events in 23vPS-Preimmunized Subjects

In 23vPS-preimmunized (≥5 years) subjects ≥70 years of age, the overall incidence of AEs as well as AEs considered related to the vaccine were similar after 13vPnC and 23vPS. Most frequent AEs were infections and infestations (4.1%) and musculoskeletal and connective tissue disorders (2.4%).

The incidences of AEs were similar after the vaccine sequences 13vPnC/13vPnC and 23vPS/13vPnC (study 3005). AEs most frequently reported after vaccination 2 of each sequence, respectively, were infections and infestations (3.3% and 4.5%) and musculoskeletal and connective tissue disorders (1.8% and 3.2%). AEs considered vaccine-related were reported in 2.6% and 1.5%, respectively. Most of these AEs were general disorders and administrative site disorders. The incidence of AEs after 13vPnC/13vPnC and 23vPS/13vPnC was similar to AEs after an initial dose of 13vPnC (study 3005). The incidence of AEs reported at the 6-month follow-up contact after vaccination 2 was also similar after vaccination 2 and vaccination 1.

5.4.3.4 Adverse Events After 13vPnC With Concomitant Administration of Trivalent Influenza Vaccine (TIV)

In 50 to 59-year-old subjects who received 13vPnC and TIV concomitantly, the incidence of AEs reported after 13vPnC+TIV was statistically significantly higher (16.7%) compared to 13vPnC alone (11.8%), whereas in subjects ≥65 years of age the incidence of AEs between the 2 groups was similar (13% and 15.8%).

The incidence of AEs after 13vPnC+TIV was similar in both age groups compared to TIV alone. In both age groups, the most frequent types of AEs were infections and infestations (3.5% to 7.7% of subjects) (studies 3001, 3008).

Vaccine-related AEs were similar for 13vPnC+TIV and 13vPnC alone ranging between 1.1% and 3.1%. The most frequently reported related AEs were events associated with vaccine administration (eg, erythema, myalgia, and headache) (studies 3001, 3008).

5.4.3.5 Adverse Events Considered Related to Study Vaccine

AEs occurring after administration of 13vPnC and considered by the investigator at least possibly related to study vaccine were reported at similar frequencies across the 6 studies (1.1% to 3.1% of subjects) regardless of subject age or 23vPS vaccination status. The types of AEs most often reported as related to study vaccine were administration site conditions.

The incidence of related AEs was similar after 13vPnC compared to 23vPS in naïve subjects 60 to 64 years old and 23vPS-preimmunized subjects ≥70 years old. Related incidences of AEs after 13vPnC+TIV were somewhat more frequent in the younger age group 50 to 59 years (3.1%) compared to the older age group ≥65 years (1.7%). Overall, incidences of related AEs after 13vPnC + TIV were low and represented events which are commonly associated with vaccination.

Similar incidences of related AEs after sequential administration of 13vPnC/13vPnC and 23vPS/13vPnC at a 1-year interval were reported in 23vPS-naïve and 23vPS-preimmunized subjects ranging from 0.6% to 2.6%.

There were only a few cases of related AEs at the 6-month follow-up contact. One (1) case of Guillain Barré syndrome developed at day 123 after 13vPnC, and was ongoing at the 6-month follow-up contact. The other cases reported were 1 case of cutaneous lupus erythematosus after vaccination with 23vPS, 1 case of injection site nodule after 13vPnC+TIV, 1 case of erythema after 23vPS/13vPnC, and 1 case of idiopathic thrombocytopenic purpura (ITP) after 23vPS/13vPnC, ongoing at the 6-month follow-up contact (see details in Section 5.4.3.7 Serious Adverse Events).

For cohort 1 of the 004 extension study with a 3.5 to 4-year interval between doses, comparisons of related AEs reported within 1 month after vaccination 2 were evaluated for the following groups: 13vPnC/23vPS vs 23vPS/23vPS, 13vPnC/13vPnC vs 23vPS/23vPS, and the 13vPnC/13vPnC vs 13vPnC/23vPS. The overall observed incidence of related AEs was very low in all groups, and slightly higher in the 23vPS/23vPS group (7 subjects, 3.7%) than in the 13vPnC/23vPS group (1 subject, 0.9%) or the 13vPnC/13vPnC group (1 subject, 0.9%), but these differences were not statistically significant. The category of related AEs which occurred

most frequently in the 23vPS/23vPS group in cohort 1 was general disorders and administration site conditions (5 subjects, 2.6%). The individual AEs included reactions at the injection site (erythema, pallor, pruritus, rash, swelling). The single related AE in the 13vPnC/23vPS group (injection site pain) was also in this category. Related AEs occurred for 1 subject in the 13vPnC/13vPnC group in cohort 1 (muscle spasm) and for 1 subject in cohort 2 (urticaria).

5.4.3.6 Deaths

During the study period, death occurred in 16 subjects in the 6 studies and the 004 extension. Nine of the 16 cases occurred in study 3005, a study with subjects ≥70 years of age. None of the deaths was vaccine-related.

Overall, the observed number of 16 deaths out of over 6000 enrolled subjects vaccinated is low.

5.4.3.7 Serious Adverse Events

Overall, the incidence of reported serious adverse events (SAEs) was low, ranging between 0.2% and 1.1% with no apparent differences among age groups or between 23vPS-naïve and preimmunized subjects. SAEs were similar after 13vPnC compared to 23vPS, 13vPnC+TIV compared to TIV or 13vPnC alone, and after sequential use of 13vPnC and 23vPS in naïve and preimmunized subjects. The most frequently reported SAEs were cardiac disorders in subjects ≥65 years of age, and musculoskeletal and connective tissue disorders in 50 to 64 year olds. SAEs were also similar at the 6-month follow-up contact after 13vPnC compared to 23vPS in 23vPS-naïve and preimmunized subjects and after concomitant administration of TIV.

After sequential use of 13vPnC and 23vPS, SAEs at the 6-month follow-up contact ranged in naïve subjects 60 to 64 years of age from 1.3% to 3.1%, and in ≥70-year-old 23vPS-preimmunized subjects between 4.3% and 5.2% due to a somewhat higher rate of cardiovascular disorders in this age group.

In general, incidences of SAEs reported at the 6-month follow-up contact were similar between 13vPnC/13vPnC and 23vPS/13vPnC in naïve 60 to 64 year olds and in preimmunized ≥70 year olds. Two (2) of the SAEs were considered by the investigator to be possibly related to the study vaccine. A 78-year-old female subject developed Guillain-Barré Syndrome on day 123 after vaccination with 13vPnC. Other possible risk factors included vaccination with influenza vaccine

given on day 29 after vaccination with 13vPnC, and an infectious origin. Varicella zoster was suspected but not confirmed. The other case was idiopathic thrombocytopenic purpura (ITP) occurring 133 days after 13vPnC in a 81-year-old male.

For cohort 1 of the 004 extension study (data submitted to the FDA on August 31, 2011), comparisons of SAEs reported within 1 month after vaccination 2 were evaluated for the following groups: 13vPnC/23vPS vs 23vPS/23vPS, 13vPnC/13vPnC vs 23vPS/23vPS, and 13vPnC/13vPnC versus 13vPnC/23vPS. Only 2 SAEs were reported (erythema multiforme 34 days after vaccination 2 in the 13vPnC/13vPnC group, and ligament rupture 39 days after vaccination 2 in the 13vPnC/23vPS group), and there were no statistically significant differences for any of the between-group comparisons. None of the subjects in cohort 2 (13vPnC/13vPnC) reported an SAE within 1 month after vaccination 2. None of the SAEs in the study 004 extension were considered related to the administered vaccine.

5.4.3.8 Withdrawals and Vaccination Discontinuations

A total of 16 subjects were withdrawn from the studies, including the 004 extension, because of adverse events. Among the subjects withdrawn because of AEs, 5 had received 13vPnC, 9 had received 23vPS, 1 had received TIV+placebo, and 1 had received placebo only. The most frequent AE type resulting in withdrawal from study was cancer.

5.4.3.9 Adverse Drug Reactions

A specific AE is identified as an adverse drug reaction (ADR) if a causal relationship between the vaccine and the AE is at least a reasonable possibility. All ADRs currently listed in the 13vPnC Core Data Sheet (CDS) for infants are kept as ADRs for adults. Data for these events from the 6 adult studies of 13vPnC were reviewed to determine their frequencies.

In addition, all AEs reported during these studies were reviewed to identify any additional ADRs. Criteria included the frequency of occurrence, the finding of a statistically significant difference in incidence between the 13vPnC and 23vPS groups, and the theoretical existence of a biologic mechanism by which the AE could be causally related to 13vPnC.

5.4.3.10 ADRs Determined for 13vPnC Adult

Frequencies for all events represent the highest frequency noted after any dose of 13vPnC for any of the 6 core studies. Although some differences were seen between 23vPS-naïve subjects and subjects previously immunized with 23vPS, the CIOMS category was the same for each of the events. A trend towards fewer adverse events was seen in subjects who were older (≥65 years old); however the CIOMS category was the same for each of the events. No differences in frequencies of adverse events were noted if 13vPnC was given as a first or second dose. In studies 004 and 3010 a direct comparison was made with 23vPS, and no major differences were seen between the 2 vaccines. Adverse reactions are listed in CIOMS frequency categories in Table 5-20:

Very common: ≥10%
Common: ≥1% and <10%
Uncommon: ≥0.1% and <1%
Rare: ≥0.01% and <0.1%
Very rare: <0.01%.

Table 5-20: 13vPnC – Adverse Reactions

Adverse Reactions	Frequencies 13vPnC 50 to 64 years	Frequencies 13vPnC ≥65 years
Injection site erythema	Very Common (20.2%)	Very Common (14.4%)
Injection site induration /swelling	Very Common (21.7%)	Very Common (12.8%)
Injection site pain/tenderness	Very Common (88.8%)	Very Common (51.7%)
Limitation of arm movement*	Very Common (42.5%)	Very Common (16.2%)
Fever	Common (7.7%)	Common (4.2%)
Decreased appetite	Very Common (25.8%)	Very Common (11.3%)
Fatigue*	Very Common (63.3%)	Very Common (34.4%)
Headaches*	Very Common (65.9%)	Very Common (26.1%)
Chills*	Very Common (24.6%)	Very Common (9.1%)

*ADRs are new to the 13vPnC adult when compared to ADRs in the 13vPnC infant program.

Table 5-14. 13vPnC - Adverse Reactions (Cont'd)

Adverse Reactions	Frequencies 13vPnC 50 to 64 years	Frequencies 13vPnC ≥65 years
Diarrhea	**The event was not solicited in this age group.**	Very Common (14.5%)
Vomiting	Common (6.9%)	Common (1.7%)
Rash	Very Common (16.5%)	Very Common (8.4%)
New muscle pain/Aggravated muscle pain*	Very Common (61.8%)	Very Common (36.8%)
New Joint pain/aggravated joint pain*	Very Common (31.5%)	Very Common (12.8%)
Nausea*	Uncommon (0.7%)	Uncommon (0.6%)
Lymphadenopathy localized to the region of the injection site	Uncommon (0.2%)	Not reported
Hypersensitivity reaction including face edema, dyspnea, bronchospasm	Uncommon (0.2%)	Uncommon (0.1%)

*ADRs are new to the 13vPnC adult when compared to ADRs in the 13vPnC infant program.

5.4.3.11 Safety in Special Groups and Situations

5.4.3.11.1 High-Risk Populations

Each trial included immunocompetent subjects with stable underlying conditions such as chronic cardiovascular disease, chronic pulmonary disease, chronic liver disease including alcoholic liver disease and alcoholism, renal disorders, and diabetes mellitus. Descriptive information on safety and reactogenicity is provided across trials. Safety and reactogenicity patterns were similar in these high-risk adults compared to the overall population of adults.

5.4.3.11.2 Age Subgroups

Safety and immunogenicity was descriptively evaluated in the 4 age subgroups, 65 to 69, 70 to 74, 75 to 79, and ≥80 years of age. Incidences for local reactions and systemic events after an initial dose of 13vPnC were similar across all 4 age subgroups and among 23vPS-naïve and 23vPS-preimmunized subjects.

A 2-vaccine sequence (second dose after 13vPnC/13vPnC and 23vPS/13vPnC) was only assessed in 23vPS-preimmunized subjects ≥70 years of age (study 3005). Incidences for local reactions and systemic events were similar after both vaccine sequences and also similar for the age subgroups 70 to 74 years, 75 to 79 years, and ≥80 years.

Incidences of serious AEs and related AEs were similar for all age subgroups after initial vaccination irrespective of immunization status, as well as after a 2-vaccine sequence, and at the 6-month follow-up contact.

5.4.3.12 Gender

5.4.3.12.1 Local Reactions

After 13vPnC, naïve and preimmunized male subjects tended to have fewer local reactions for all types of local reactions compared to female subjects (studies 004, 3005). After a 2-vaccination sequence (13vPnC/13vPnC and 23vPS/13vPnC) in preimmunized subjects, also fewer local reactions were reported for male compared to female subjects. However, within each gender group, incidences were similar (study 3005).

5.4.3.12.2 Systemic Events

After 13vPnC in naïve subjects, the incidence of fever was similar in male and female subjects, whereas for the other types of systemic events male subjects tended to have lower incidences. After 13vPnC in preimmunized subjects, all types of systemic events, including fever, were similar (study 3005).

In preimmunized subjects after the vaccination sequence 13vPnC/13vPnC, systemic event incidences were similar between genders; however, after 23vPS/13vPnC the majority of systemic event types was higher for female subjects compared to males; the most frequent occurrences being new muscle pain (45% and 25%), fatigue (43.9% and 24.8%), and headache (29.8% and 15.3%) (study 3005).

5.4.3.12.3 Adverse Events

AEs after an initial dose of 13vPnC and 23vPS were similar between naïve and preimmunized male and female subjects. AEs after 2 vaccine sequences (13vPnC/13vPnC and 23vPS/13vPnC) in preimmunized subjects were similar for male and female subjects. Related AEs were similar

between gender and naïve and preimmunized subjects. AEs after an initial dose of 13vPnC and 23vPS at the 6-month follow-up contact were similar between male and female subjects but somewhat higher in preimmunized compared to naïve subjects (19.8% and 3.6%).

AEs after both vaccine sequences (13vPnC/13vPnC and 23vPS/13vPnC) at the 6-month follow-up contact, were reported slightly more frequently for male subjects (12.6% and 17.3%) compared to female subjects (9.2% and 6.9%), due to somewhat higher incidences of cardiac disorders, gastrointestinal disorders, and musculoskeletal disorders in male subjects.

5.4.3.12.4 Serious Adverse Events

In naïve and preimmunized subjects, SAEs after an initial dose of 13vPnC were very low (male <1.2%, female < 0.4%), and similar between gender groups at the 6-month follow-up contact.

SAEs after 2 vaccine sequences (13vPnC/13vPnC and 23vPS/13vPnC) in preimmunized subjects were similar for male and female subjects.

SAEs after the 2 vaccine sequences (13vPnC/13vPnC and 23vPS/13vPnC) at the 6-month follow-up contact were slightly more frequent in male (5.8% and 7.4%) compared to female subjects (2.7% and 3.0%) due to somewhat more frequently reported cardiac disorders, infections and infestations, and neoplasms in male subjects.

5.5 Safety Conclusions

Based on the results of the 6 clinical studies, including the study 004 extension, the safety and reactogenicity profile of 13vPnC has been shown to be acceptable and comparable to 23vPS in 23vPS-naïve subjects; subjects preimmunized with 23vPS showed an improved safety and reactogenicity profile after vaccination with 13vPnC compared to revaccination with 23vPS.

Overall, safety and reactogenicity data indicate that subjects naïve to 23vPS can be safely vaccinated with 13vPnC. A second dose of 13vPnC given at a 1-year or 3.5 to 4-year interval, does not increase reactogenicity (13vPnC/13vPnC). In contrast, administration of a study dose of 23vPS to adults ≥70 years of age previously immunized at least 5 years earlier with 23vPS, or administration of 13vPnC followed by 23vPS one year later (13vPnC/23vPS) in younger adults showed higher local reactogenicity and an increase for some systemic reactions. Local reactions

after a second dose of 23vPS in the regimen 23vPS/23vPS administered 3.5 to 4 years apart were generally higher after the second dose. The incidences of individual local reactions were, in general, lower for subjects in the 13vPnC/13vPnC and 13vPnC/23vPS groups than for subjects in the 23vPS/23vPS group, when vaccines were administered 3.5 to 4 years apart. Systemic events after 13vPnC/13vPnC and 13vPnC/23vPS were generally comparable to those after the first dose, with 3.5 to 4-year interval between doses, and were generally comparable or lower than rates after 23vPS/23vPS.

The common feature for each of the immunization regimens associated with higher reaction rates is receipt of 23vPS with its high pneumococcal polysaccharide load (25 µg for each polysaccharide) in a setting of pre-existing antibody from prior 13vPnC or 23vPS vaccination. This high polysaccharide load in the setting of prior antibody is likely to be responsible for the increased reactions seen. Higher pre-existing antibody titers have been associated with increased reactions after 23vPS vaccine whether present at the time of initial vaccination or at revaccination.[1]

Subjects vaccinated with 23vPS followed 1 year later by 13vPnC (23vPS/13vPnC) showed an acceptable safety profile, indicating that 23vPS-preimmunized subjects could be safely vaccinated with 13vPnC, even at a stringent 1-year interval, if needed. When subjects had an interval of 5 or more years between the 23vPS dose and a 13vPnC dose, the safety profile of 13vPnC was similar or even improved compared to the 1-year interval. Overall, subjects preimmunized with 23vPS had significantly fewer local and systemic events when vaccinated with 13vPnC compared to revaccination with 23vPS. It was also shown that preimmunized subjects vaccinated with 13vPnC can safely receive a second dose of 13vPnC. Those revaccinated with 23vPS may also safely receive a subsequent dose of 13vPnC if needed.

Coadministration of 13vPnC with TIV was well tolerated although somewhat more local and systemic events were observed in the younger subjects (50 to 59 years) compared to older subjects (≥65 years). Higher trends or statistically higher rates were seen for some systemic events after concomitant use but were judged to fall within a satisfactory safety profile for concomitant use.

6.0 POST-APPROVAL PLANS

6.1 Safety Assessments

Additional safety data will be provided from the CAPITA study (6115A1-3006-NL), which began in 2008 and is currently ongoing. The study is a phase 4, randomized, placebo-controlled clinical trial of 13vPnC efficacy in the prevention of vaccine-serotype pneumococcal CAP and IPD. Subjects ≥65 years who are naïve to pneumococcal vaccination are randomly assigned in a 1:1 ratio to receive either 13vPnC or placebo.

Approximately 85,000 subjects (42,500 in each group) were to be randomly assigned in this study. Subjects were to be enrolled at multiple sites in regions throughout the Netherlands by the Julius Center. Two thousand (2000) subjects (1000 in each group) were to be recruited from 1 of the regions and randomly assigned in the immunogenicity subset. The immunogenicity subset was to be stratified by age; at least 300 subjects were to be enrolled in each of the following age groups: 65 to 69, 70 to 79, and ≥ 80 years.

A medical history was to be performed for all subjects to establish eligibility. SAEs were to be reported during the following periods:

- after administration of blinded 13vPnC/placebo at visit 1, from signing of the informed consent form (ICF) to 28 days after vaccine administration for subjects not in the immunogenicity subset.
- after administration of blinded 13vPnC/placebo at visit 1, from signing of ICF to 6 months after vaccine administration for subjects in the immunogenicity subset.
- at administration of 13vPnC to subjects in the placebo group, if this occurs, from signing of ICF to 28 days after vaccine administration.

Deaths were to be recorded from signing of ICF to the end of the case acquisition period.

Additional safety assessments were to be performed in subjects in the immunogenicity subset.

Reactogenicity events are predefined AEs that could occur after vaccine administration and are considered solicited AEs. They are as follows:

- Local reactions: pain, redness, swelling, and limitation of arm movement.
- Systemic events: fever (oral temperature ≥38°C), diarrhea, chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain.

Reactogenicity events were to be recorded and reported from the time of study vaccine administration for 7 days (days 1 to 7). Events lasting longer than 7 days after vaccination were required to be followed until the events subsided, returned to baseline, or in case of permanent impairment, until the condition stabilized. Local reactions, systemic events, and use of antipyretics and pain medication for treatment of pain at the study vaccine injection site was to be collected in the 7 days (days 1 to 7) following test article administration using an e-diary. The end dates of each reactogenicity event were required to be recorded. In addition, AEs were to be documented in the case report form (CRF) and reported from the signing of the ICF until 28 days after test article administration (day 29). These additional AEs are referred to as unsolicited AEs.

If efficacy is demonstrated and 13vPnC is offered to subjects in the placebo group, SAEs will be recorded until 28 days after 13vPnC administration.

6.2 Effectiveness

Surveillance for IPD will be conducted by the US Centers for Disease Control and Prevention (CDC) using the Active Bacterial Core surveillance (ABCs) system. The ABC is a population-based, national surveillance system for pneumococcal disease in 10 states covering approximately 28 million people throughout the United States. The ABC surveillance system is funded and staffed by the US CDC, and provides analysis independent from Pfizer.

The overall objectives of the ABC surveillance system are:

- To determine the incidence and epidemiologic characteristics of invasive disease due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, group A

streptococcus, group B streptococcus, and methicillin-resistant *Staphylococcus aureus* in multiple large diverse US populations.

- To determine molecular epidemiologic patterns and microbiologic characteristics of public health relevance for isolates causing the above invasive infections.
- To provide an infrastructure for further research, such as special studies aimed at identifying risk factors for disease, post-licensure evaluation of vaccine efficacy, and monitoring effectiveness of prevention policies.

The specific objectives of the ABC surveillance program for *Streptococcus pneumoniae* surveillance are:

- To track emerging antimicrobial resistance in pneumococcal isolates.
- To evaluate the impact of new pneumococcal conjugate vaccines for infants on disease burden and on antimicrobial resistance.
- To evaluate prevention among the elderly through pneumococcal polysaccharide vaccine use.

The ABC surveillance program can determine the effectiveness against invasive pneumococcal disease for all serotypes in the vaccine. In addition to the ABC surveillance system, several other surveillance systems in the US and internationally have contributed important information to understanding the effects of 7vPnC vaccination programs, and data collection is ongoing to assess the effectiveness of 13vPnC in infants and young children.

Additional details of the CAPITA trial and other studies are included in Appendix 1.

7.0 OVERALL CONCLUSIONS

The data from the pivotal clinical trials support the following perspectives on the use of 13vPnC in adults:

- 13vPnC elicits an improved immune response compared to 23vPS when administered to pneumococcal vaccine-naïve adults ≥50 years of age.

- 13vPnC elicits an improved immune response compared to 23vPS and is the preferred choice for reimmunization to enhance protection for adults ≥70 years of age who have been previously immunized with 23vPS.
- Whenever possible, 13vPnC should be administered first to pneumococcal vaccine-naïve and 23vPS-experienced adults to take full advantage of the immunologic benefit afforded by the conjugate vaccine. 13vPnC establishes immune memory and permits revaccination to maintain an optimum functional anti-pneumococcal antibody response in both pneumococcal vaccine-naïve and -experienced adults. 13vPnC permits immunization to begin at 50 years of age and continue over an extended period of risk. By contrast, 23vPS fails to induce immunologic memory, has a negative immunologic impact on a second dose, and is therefore likely incapable of providing durable protection or comparable protection with revaccination.
- Serotype-specific IgG and OPA immune responses to 13vPnC administered concomitantly with TIV were lower for at least some serotypes compared to responses when 13vPnC was given alone in adults 50 to 59 years of age and adults ≥65 years of age. Concomitant use of 13vPnC and TIV should be dictated by clinical circumstances.
- The safety profile of 13vPnC is acceptable in pneumococcal vaccine-naïve and pneumococcal vaccine-preimmunized adults.

In conclusion, the 13vPnC vaccine has met the requirements for licensure as agreed with both US and EU regulators. In addition, the specific requirement set forth by the FDA to demonstrate potential benefit for older adults who have previously been vaccinated with the 23vPS vaccine was met. The immunologic data support the likelihood that 13vPnC will address the unmet medical need of providing greater protection against pneumococcal disease, including community-acquired pneumonia, over a longer age range of adult risk. These observations and conclusions support the introduction of 13vPnC into the public health system to satisfy an important unmet medical need for protection of adults against pneumococcal disease, prior to completion of the confirmatory community-acquired pneumonia efficacy trial.

8.0 APPENDIX

8.1 Appendix: Additional Ongoing Studies

8.1.1 Efficacy Study Against Community-Acquired Pneumonia (CAPITA, Study 6115A1-3006)

This study was designed to provide eventual evidence of the effectiveness of 13vPnC for the prevention of pneumococcal disease, including IPD and non-bacteremic CAP. The study is large and complex, and involves the use of a newly developed diagnostic assay for the vaccine-specific pneumococcal serotypes. Final results from the study are not expected for some time and, when available, will be submitted as a supplement/variation to the license initially obtained on the basis of surrogate immunogenicity.

The **C**ommunity-**A**cquired **P**neumonia **I**mmunization **T**rial in **A**dults (**CAPITA)** was begun in the fall of 2008. The primary clinical objective of the CAPITA trial is to establish the efficacy of the 13vPnC vaccine in the prevention of a first episode of vaccine serotype-specific pneumococcal CAP in community-dwelling adult persons aged ≥65 years. As secondary objectives, the study aims to establish the efficacy of 13vPnC in the prevention of a first episode of non-bacteremic non-invasive vaccine-type (VT) pneumococcal CAP and a first episode of VT-IPD. In addition, the study will evaluate the safety profile of the vaccine as assessed by monitoring of SAEs for 1 month after immunization and deaths for the duration of the study. Immunogenicity and nasopharyngeal carriage will be evaluated in a subset of 2000 participants. SAEs will be monitored for 6 months in this subset.

The CAPITA study targeted up to 85,000 study subjects (randomly assigned 1:1 to receive either 13vPnC or placebo) for enrollment from community dwelling adult persons ≥65 years, with an estimated drop out rate of 5%. Subjects are to be followed up for VT-CAP events and IPD for approximately 2 years after completion of enrollment.

The occurrence of the primary outcome of VT-CAP will be established based on 3 sets of criteria: (1) a clinical definition of CAP; (2) independent interpretation of chest radiograph consistent with pneumonia; and (3) determination of *S pneumoniae* serotype. Identification of *S pneumoniae* as the definite causative agent of CAP relies on blood cultures and positive

urinary antigen detection. An independent data monitoring committee (DMC) was implemented for the study to review safety data and reports. The rationale and design of the CAPITA study has been published.[159]

8.1.2 Revaccination of Adults After 5 Years (6115A1-3001)

After the dose of placebo or TIV/13vPnC given in the second month of study 3001, subjects are to be followed up for a further 5 years. Annual bleeds are to be obtained to assess the decline of antibodies over time. At year 5, subjects will be vaccinated with a second dose of 13vPnC and the immune response and tolerability will be assessed. This study will not only provide data on the kinetics of the response, but also on the potential value of revaccination 5 years after the initial vaccination. These data are estimated to be available in 2014 in sufficient time to provide guidance for adults immunized at the time of anticipated licensure in 2011, for whom a 5-year interval for possible 13vPnC reimmunization would be in 2016.

8.1.3 Antibody Persistence Study (6115A1-3018)

Study 6115A1-3001 provided data on longevity of antibody response in 23vPS-naïve subjects 50 to 59 years of age. The 6115A1-3005 non-inferiority trial, comparing antibody responses to 13vPnC or 23vPS in 23vPS-immunized adults ≥70 years of age, affords an opportunity to extend follow up of this population to determine whether differences exist in antibody decline that would favor administration of 13vPnC in a 23vPS-preimmunized population. Likewise, extended follow up of subjects 60 to 64 years of age at the time of initial immunization in study 6115A1-3010 would permit a descriptive evaluation of antibody levels after a regimen of 13vPnC/23vPS, 13vPnC/13vPnC, or 23vPS/13vPnC spaced 1 year apart. 23vPS-naïve and preimmunized subjects from studies 6115A1-3005 and 6115A1-3010, respectively, were to be enrolled in study 6115A1-3018 and blood samples were to be taken 1 year later to evaluate the persistence of the antibody response.

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